# Canagliflozin
## Advisory Committee Meeting

**Endocrinologic and Metabolic Drugs**

**Advisory Committee**

**January 10, 2013**

# Introduction

**Jacqueline Coelln-Hough, R.Ph.**
Janssen Research & Development, LLC

# Canagliflozin
# Drug Class and Indication

- **New Class**
  - Sodium glucose co-transporter 2 (SGLT2) inhibitor
  - Insulin independent mechanism
- **Proposed Indication**
  - an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- **Proposed dose and administration**
  - 100 or 300 mg tablet once daily
    - With specific recommendations for patients who should start with 100 mg

# Canagliflozin
# Clinical Development Program

- **Largest T2DM program submitted to Health Authorities to date**
  - 10,301 subjects enrolled in Phase 3
- **Long duration of treatment**
  - > 2800 subjects treated with canagliflozin ≥ 18 months
    (as of 01 July 2012 )
- **Studies at each step of the treatment paradigm**
- **Significant experience in vulnerable populations (> 50 % Phase 3)**
  - Long standing diabetes: mean 10.6 years
  - Age
    - ≥ 65 years: >3000 subjects
    - ≥ 75 years: >500 subjects
  - Renal impairment: > 1000 subjects
  - CV disease: >4000 subjects

# Canagliflozin

The totality of the data supports that canagliflozin:

- Provides substantial glucose control with the added benefits of weight loss and BP reduction
- Has a safety profile that is characterized across the full continuum of patients with T2DM
- Has adverse drug reactions that can be managed
- Both the 100 and 300 mg doses provide a valuable additional treatment option to address the unmet medical need

# Sponsor Presentation Agenda

| | |
|---|---|
| **Introduction** | **Jacqueline Coelln-Hough, RPh**<br>Janssen Research & Development, LLC<br>Senior Director, Global Regulatory Affairs |
| **Medical Landscape & Unmet Need** | **Edward Horton, MD**<br>Senior Investigator, Joslin Diabetes Center, Boston<br>Professor of Medicine, Harvard Medical School<br>Past-President ADA |
| **Mechanism of Action, Phase 3 Program Overview & Efficacy** | **Gary Meininger, MD**<br>Janssen Research & Development, LLC<br>Franchise Medical Leader |
| **Safety & Tolerability** | **Peter Stein, MD**<br>Janssen Research & Development, LLC<br>Head of Metabolism Development |
| **Benefit-Risk Review** | **John Gerich, MD**<br>Professor Emeritus,<br>University of Rochester, New York |

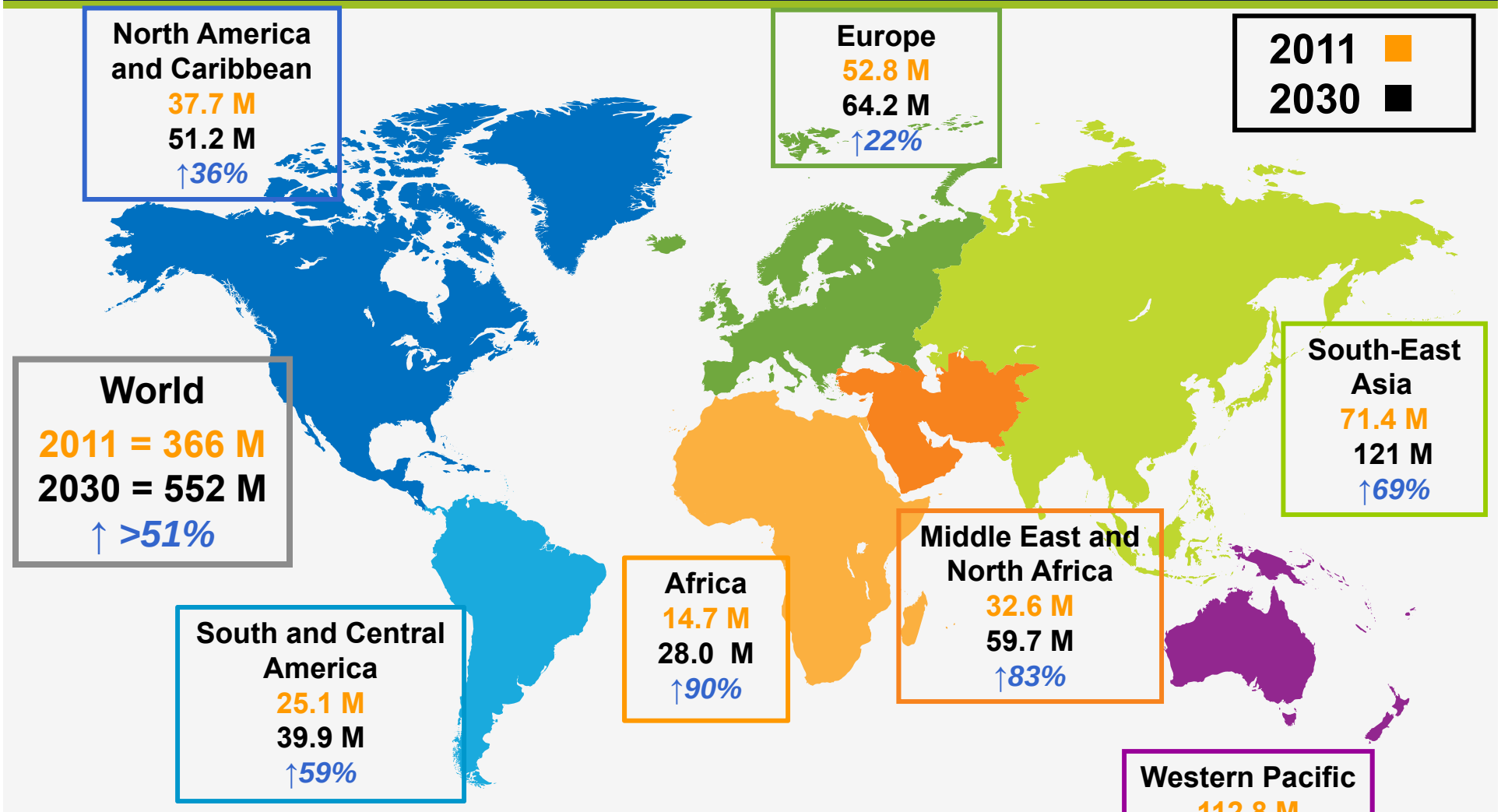
# Consultants Available to the Committee

| Participant | Expertise and Affiliation |
|---|---|
| **George Bakris, MD** | **Nephrology**<br>Professor of Medicine , University of Chicago |
| **John Bilezikian, MD** | **Metabolic Bone Disease**<br>Professor of Medicine & Pharmacology<br>Columbia University College of Physicians and Surgeons |
| **Samuel Cohen, MD, PhD** | **Oncology**<br>Professor, Department of Pathology & Microbiology, University of Nebraska Medical Center |
| **Greg Fulcher, MD** | **Chairman of the Endpoint Adjudication Committee**<br>Clinical Professor of Medicine<br>University of Sydney |
| **Peter Kowey, MD** | **Cardiovascular**<br>Professor of Medicine & Clinical Pharmacology,<br>Thomas Jefferson University |
| **David Matthews, MD** | **Chairman of the CANVAS Steering Committee**<br>Professor of Diabetes<br>Oxford Center for Diabetes, Endocrinology & Metabolism |
| **Paul Watkins, MD** | **Hepatology**<br>Professor of Medicine, University of North Carolina Health Care System |

# Medical Landscape

**Edward Horton, MD**
Joslin Diabetes Center, Harvard Medical School, Boston

# Global Projections for the Diabetes Epidemic: 2011–2030



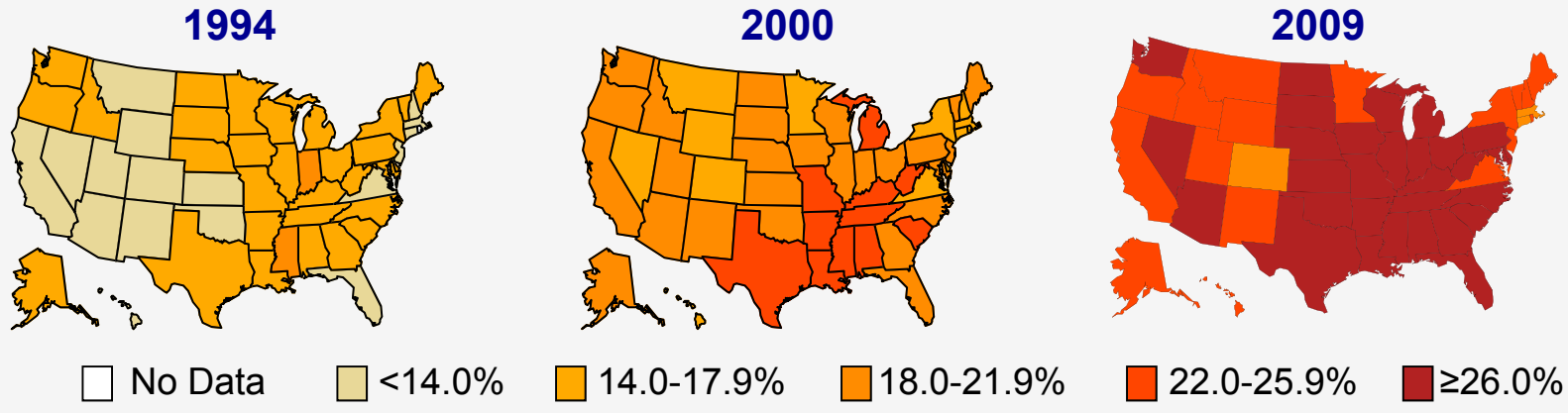

M = million

Diabetes Atlas Committee. *Diabetes Atlas 5th Edition:* IDF 2011.

# Increased Obesity has Led to Increased Type 2 Diabetes

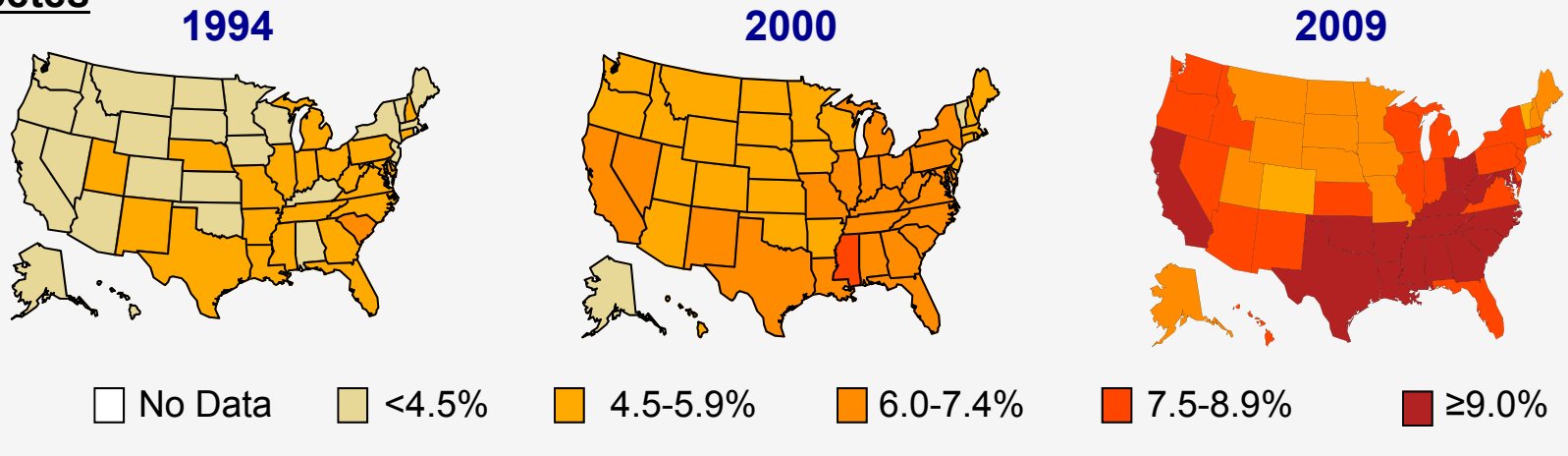
**Obesity (BMI ≥30 kg/m²)**

OBESITY




**Diabetes**

DIABETES




CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

# The Dual Epidemic: Obesity and Diabetes

- 65% of adult Americans are overweight (BMI >25) and 32% are obese (BMI >30)
- There are now an estimated 25.8 million people with DM in the USA (11.3% of adults) and 79 million with pre-diabetes (IFG/IGT)
- The lifetime risk of developing DM for people born in 2000 is 33% for men and 39% for women

# Economic Costs of Diabetes

- Total direct and indirect costs of diabetes in the USA (2007): $174 billion*. Direct costs $116 billion, indirect costs $58 billion
- Diabetes is the leading cause of blindness in adults, the leading cause of kidney failure and of non-traumatic lower limb amputations.
- 60-70% of people with diabetes have mild to severe neuropathy
- The risk of heart disease and stroke is 2-4x greater in people with diabetes than without

National Diabetes Information Clearing House National Diabeters Statistics 2011
*Diabetes Care **March 2008** vol. 31 no. 3 **596-615**

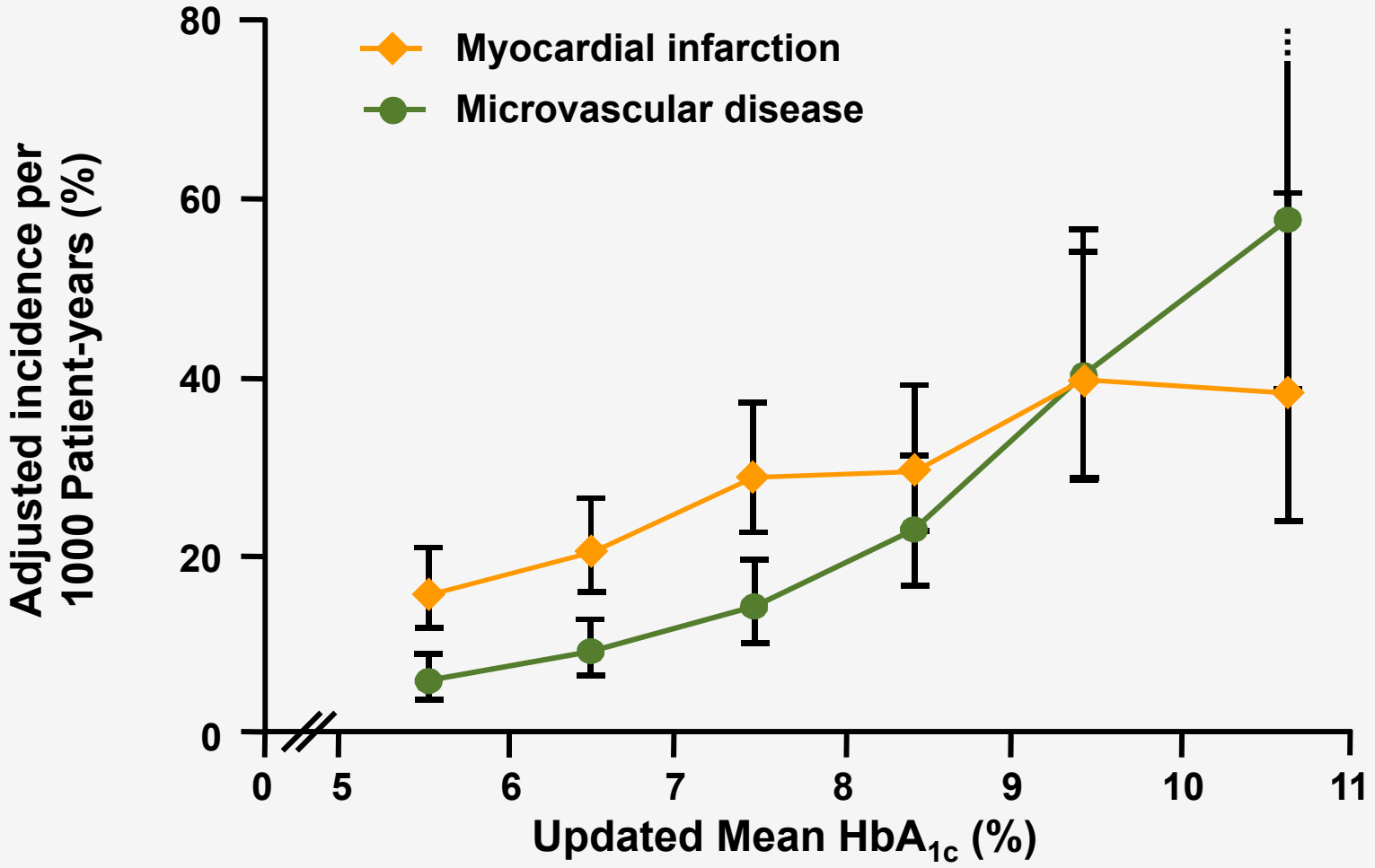
# Lowering $HbA_{1c}$ Reduces Complications in Type 1 and Type 2 Diabetes

| $HbA_{1c}$ | DCCT<br>9.1% → 7.3% | Kumamoto<br>9.4% → 7.1% | UKPDS<br>7.9% → 7.0% |
|---|---|---|---|
| Retinopathy | ↓ 63% | ↓ 69% | ↓ 17%–21% |
| Nephropathy | ↓ 54% | ↓ 70% | ↓ 24%–33% |
| Neuropathy | ↓ 60% | Significantly improved | — |
| Macrovascular disease | ↓ 41%* | — | ↓ 16%* |

***Not statistically significant**

DCCT Research Group. *N Engl J Med*. 1993;329:977-986. Ohkubo Y, et al. *Diabetes Res Clin Pract*. 1995;28:103-117. UKPDS Group. *Lancet*. 1998;352:837-853.

# Glycemia in Relation to Microvascular Disease and Myocardial Infarction




Stratton IM et al. *BMJ*. 2000;321(7258):405-412.

# Glycemic Goals for Diabetes Management

| | NORMAL | GOAL |
|---|---|---|
| **AMERICAN DIABETES ASSOCIATION** | | |
| $HbA_{1c}$ (%) | < 6 | < 7* |
| **AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY (AACE/ACE)** | | |
| $HbA_{1c}$ (%) | < 6 | ≤ 6.5 |

* $HbA_{1c}$ goal for individual patient is as close to normal (<6%) as possible without significant hypoglycemia

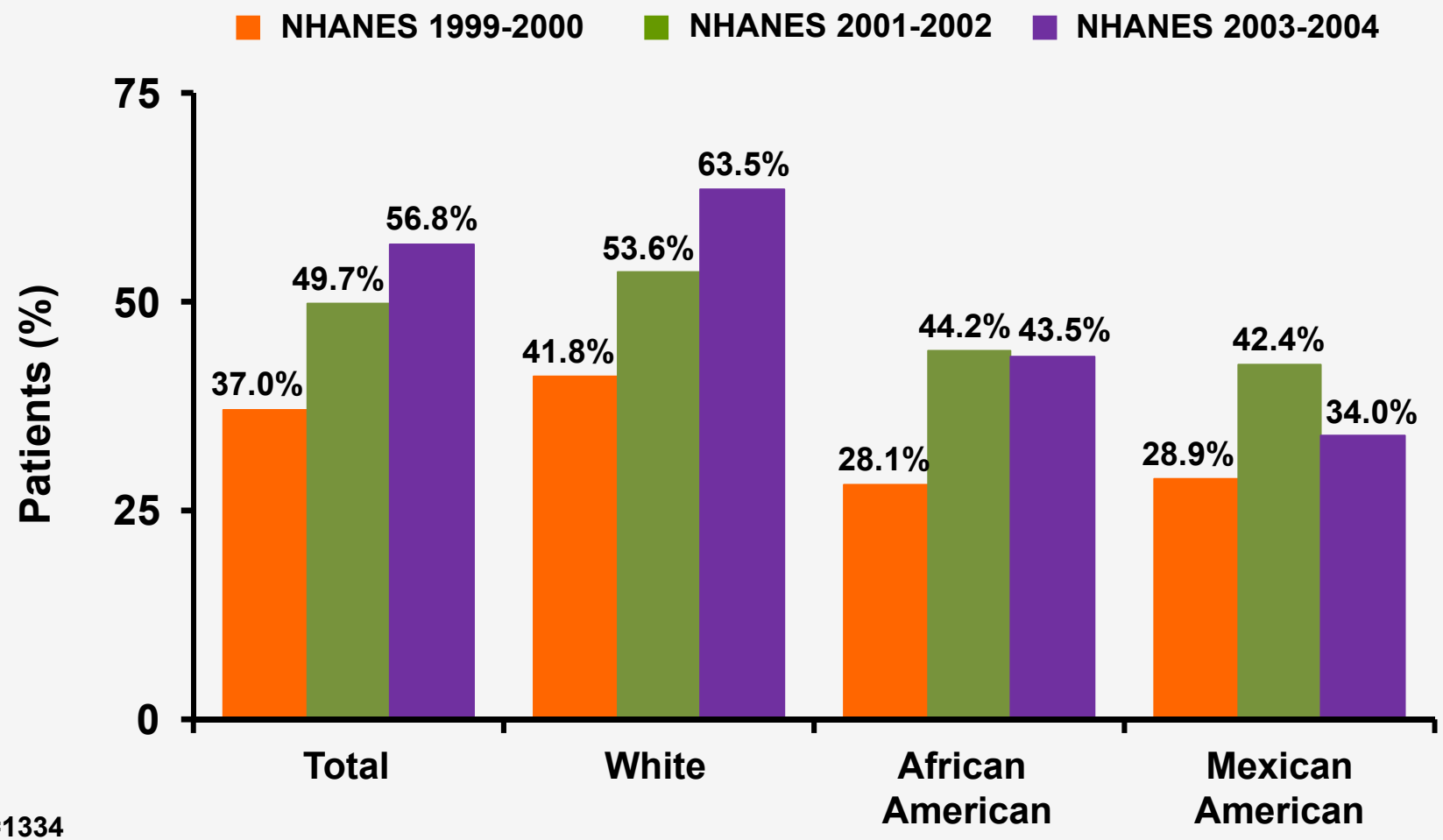
American Diabetes Association. Diabetes Care. 2007 Jan 1; 30(suppl_1):S4-41.

American College of Endocrinology Consensus Conference on Guidelines for Glycemic Control. August 2001, Washington, DC.

# The Need for Individualization of Treatment Approaches and Goals

- Intensive management – with tight glycemic control – can have dramatic and long-term benefits
- *However*, late introduction of tight control in older patients with CVD (as in ACCORD), may have risks
- The key is individualization of therapy – based upon age, life expectancy, presence of complications, co-morbidities (including CVD), other patient factors, risks/impact of hypoglycemia, all must be considered

# Glycemic Control Has Improved – But Many Patients Still Not at Goal $HbA_{1c}$ <7%

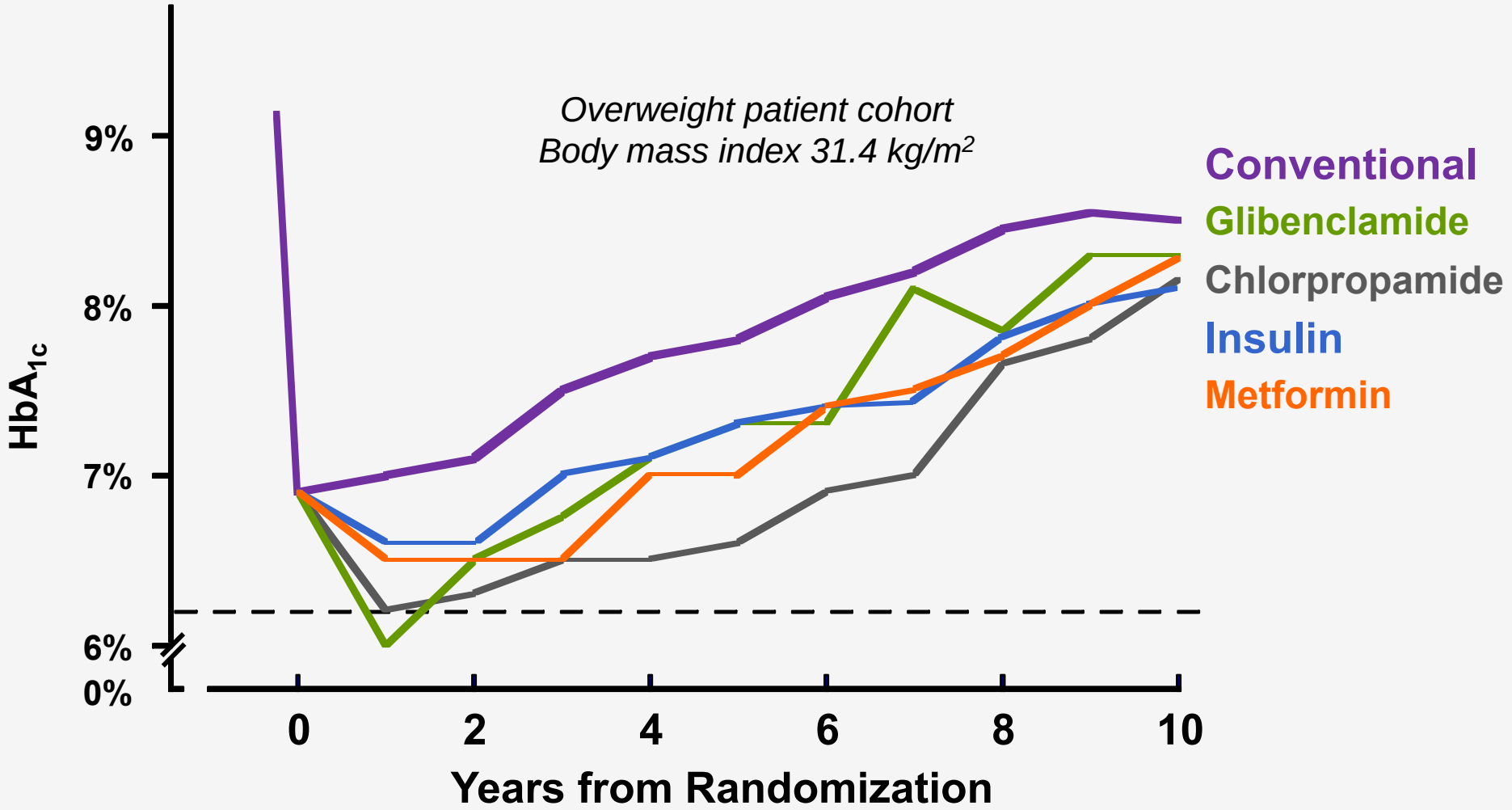



**N=1334**
**NHANES=National Health and Nutrition Examination Survey**

Data from Ford E, et al. *Diabetes Care*. 2008;31(1):102-104.

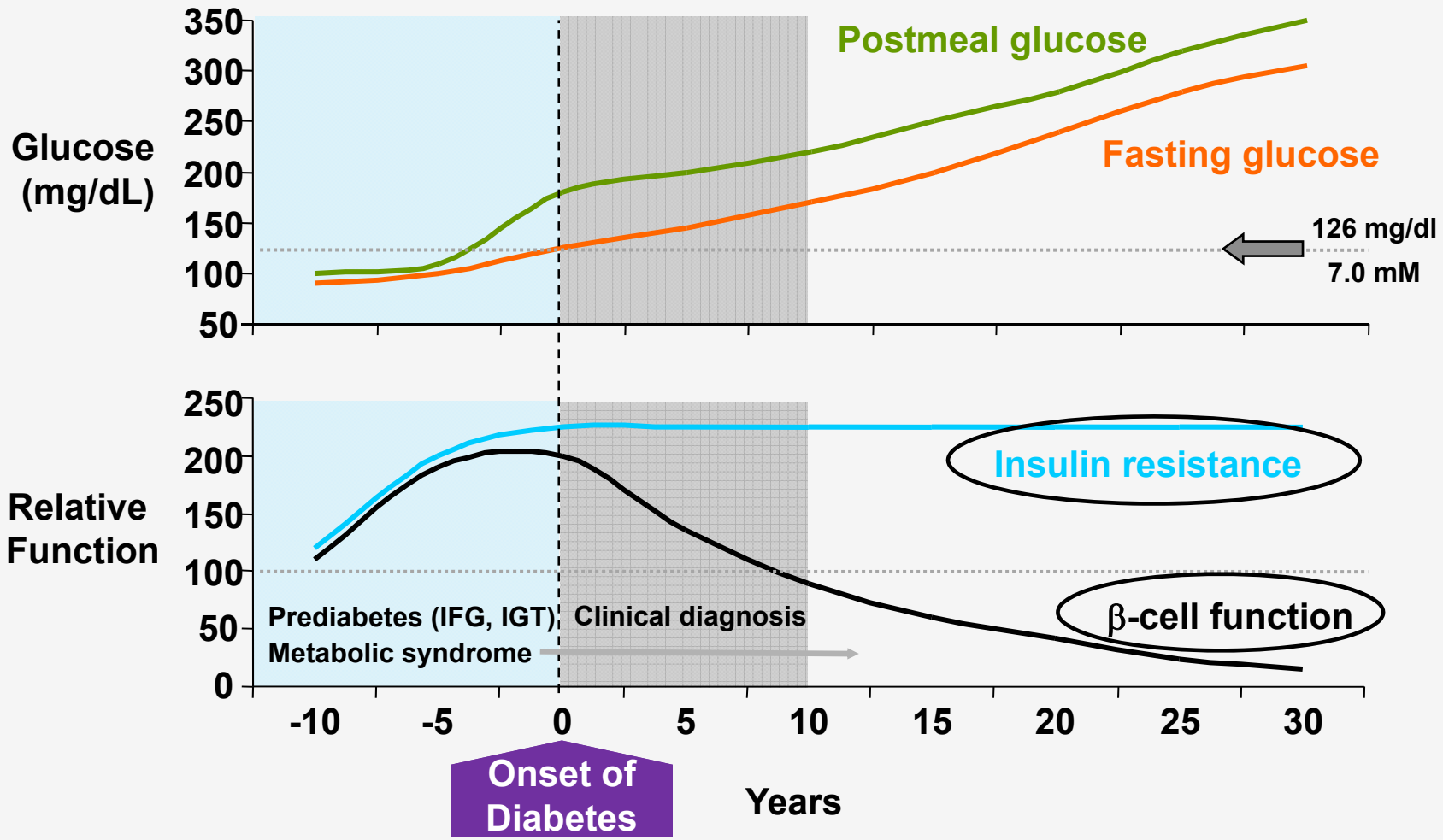
# UKPDS Head to Head Therapy Comparison: Progressive Deterioration with All Agents

Progressive HbA1c deterioration – due to progressive loss of insulin secretion

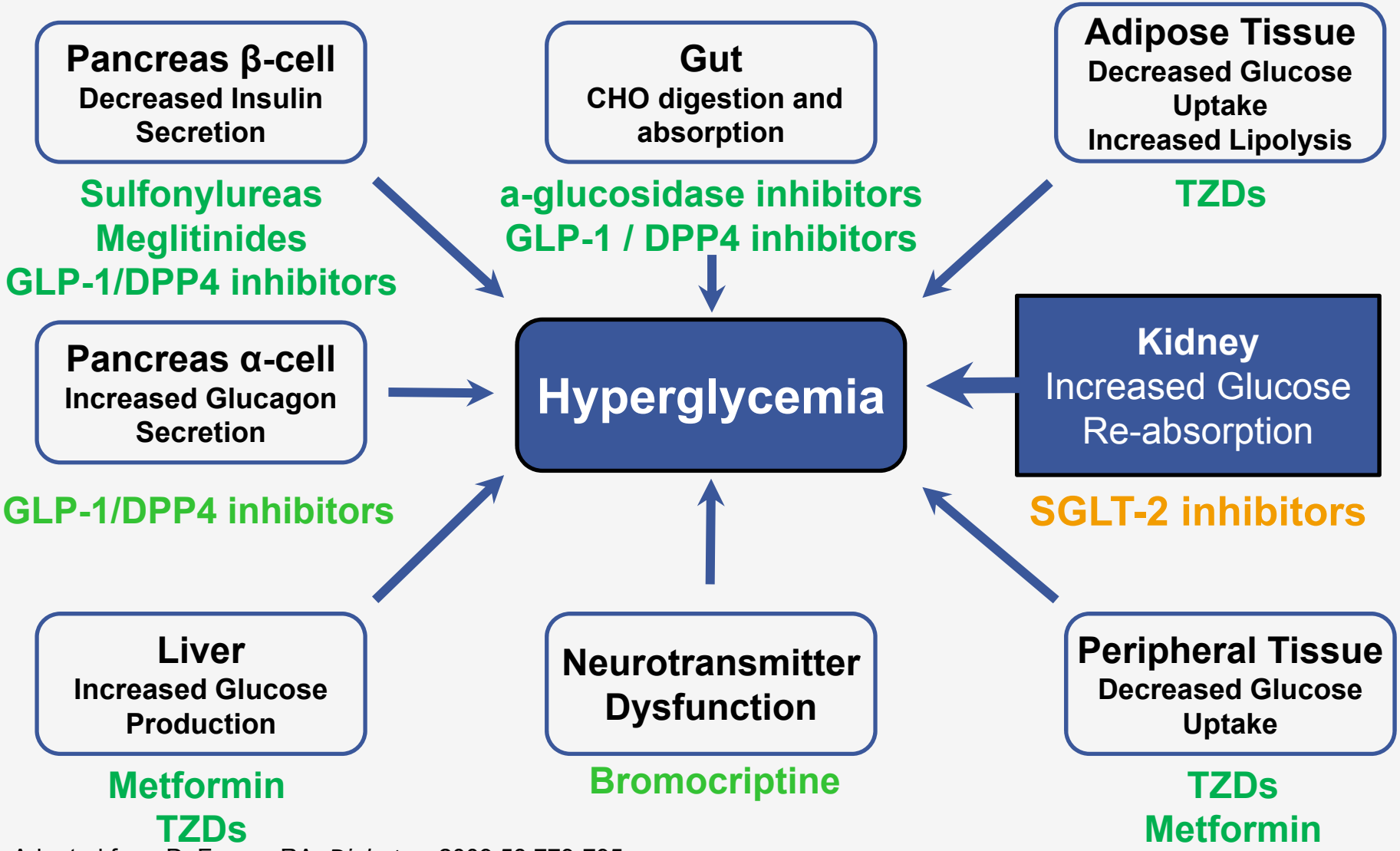



*UKPDS 34. Lancet 1998; **352**: 837-853*

# Natural History of Type 2 Diabetes



# Pathophysiology and Pharmacotherapy of Hyperglycemia in Type 2 Diabetes




Adapted from DeFronzo RA. *Diabetes.* 2009;58:773-795.

# Limitations of Current Treatments for Patients with T2DM

- 5 classes of oral agents – 2 classes of SQ agents are recommended by ADA/EASD
- Limitations of currently available classes
  - Limited efficacy or durability: sulphonylurea (SU) agents, DPP-4 inhibitors
  - Hypoglycemia: SU agents, insulin
  - Weight gain: SU agents, PPARγ agents, insulin
  - GI side effects: metformin, GLP-1 agonists
  - Fluid retention: SU agents, PPARγ agents, insulin

<u>Conclusion: there is a need for new agents / new options</u>

# Imperative for New AHAs

- Diabetes is a rapidly advancing epidemic
  - Failure to adequately control hyperglycemia can have devastating consequences on affected individuals and on society

- Currently available AHAs have limitations (wt gain, GI side effects, limited efficacy and/or long-term durability)
  - Many patients not achieving or maintaining HbA1c goal of < 7%

# Mechanism of Action

**Gary Meininger, MD**

Franchise Medical Leader - Metabolism

Janssen Research and Development

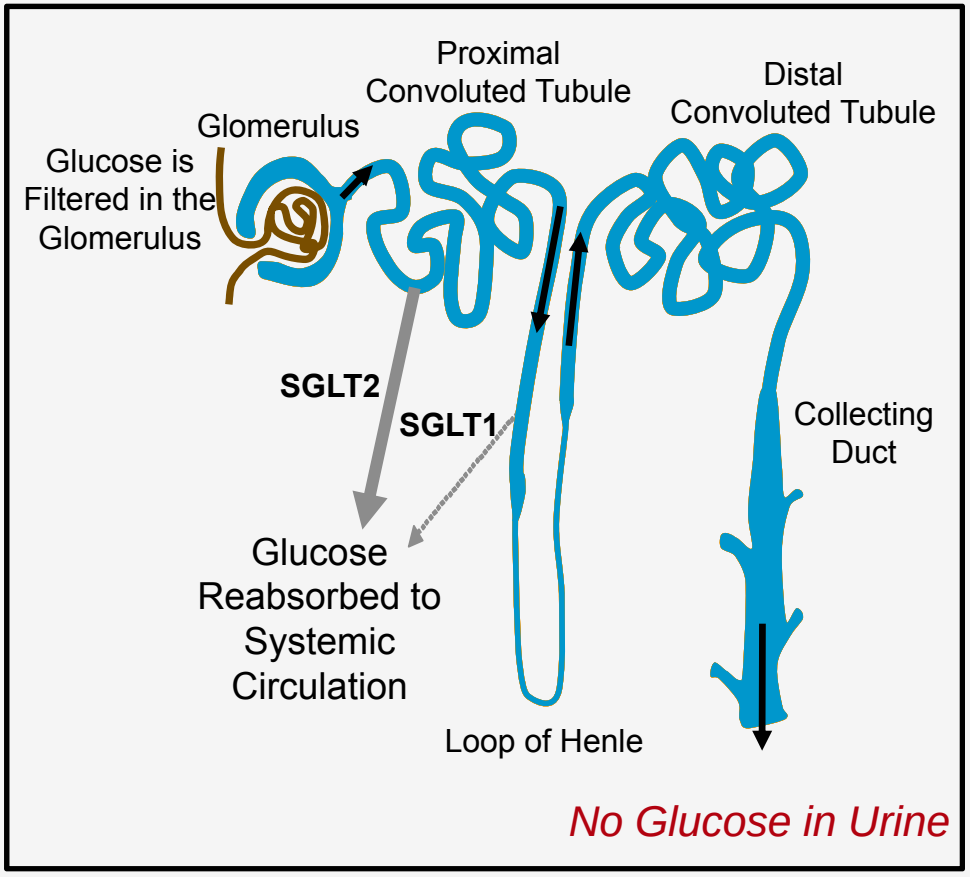
# Sodium-glucose Transporter-2 (SGLT2): Key Renal Transporter Reabsorbing Filtered Glucose Back into Systemic Circulation

## SGLT2

- Primarily expressed in kidney
- Responsible for majority of renal glucose reabsorption

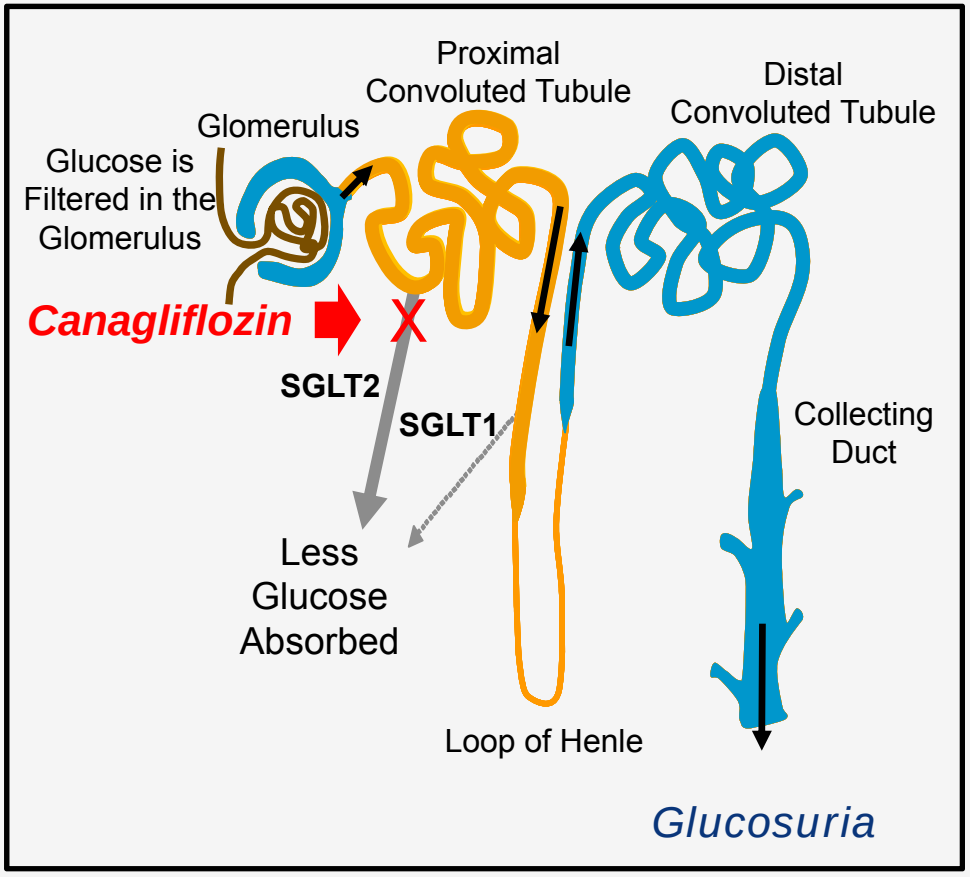
## SGLT1

- Responsible for small portion of renal glucose reabsorption
- Prominent role in intestinal glucose absorption

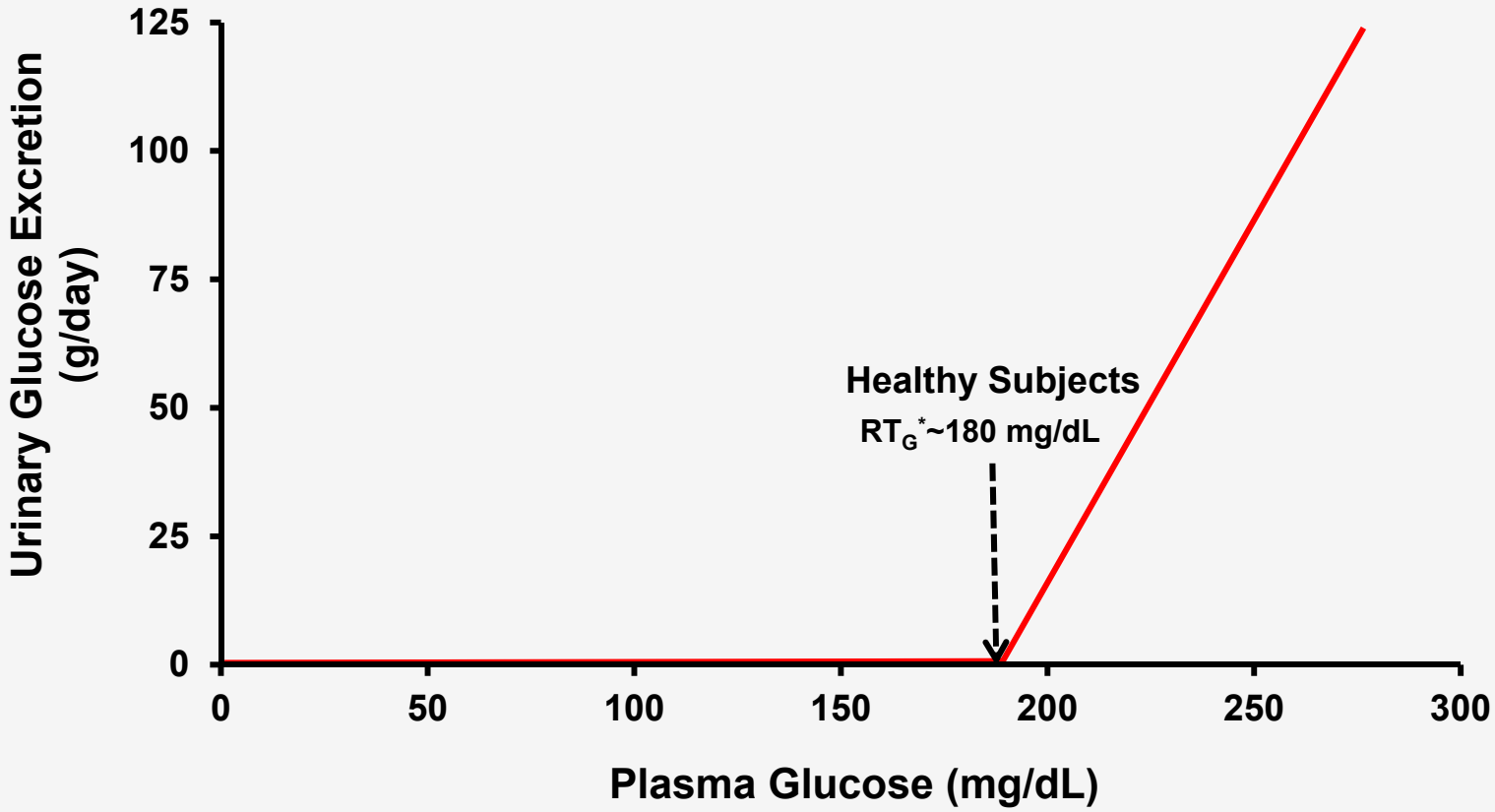


# Canagliflozin: SGLT2 Inhibition Leads to Improved Glucose Control in T2DM

- CANA is potent, selective inhibitor of SGLT2
- UGE ~ 80-100 grams/day, thereby reducing plasma glucose
- Additional contributors to glucose control
  - Reduction in body weight due to 300-400 kcal/day loss to UGE
  - Improved beta-cell function
- Mechanism of action independent of insulin

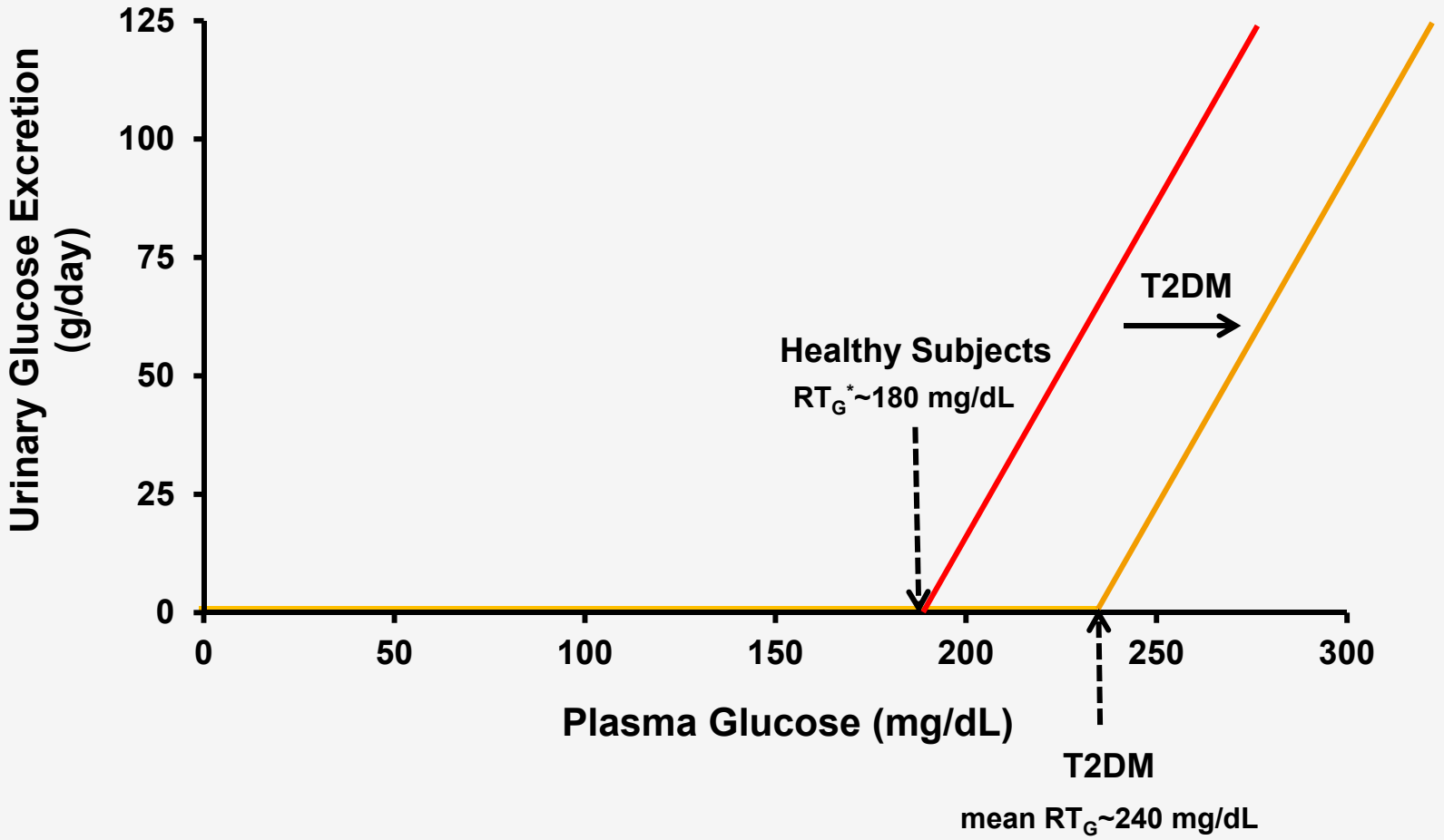


# There is a Threshold Relationship Between Plasma Glucose and UGE



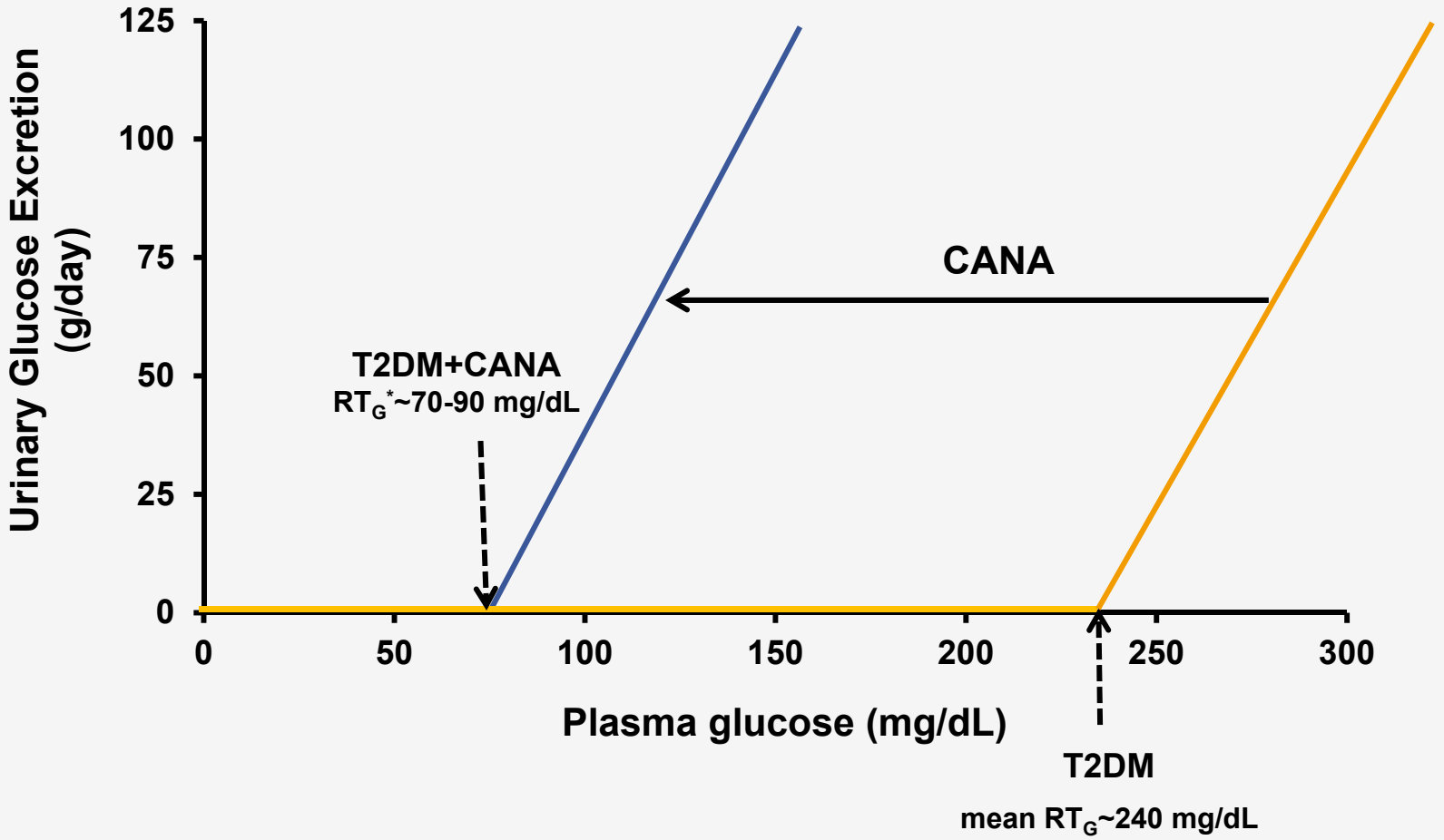

*Renal threshold for glucose

# Renal Glucose Reabsorption and $RT_G$ are Elevated in T2DM




*Renal threshold for glucose

# Canagliflozin Lowers $RT_G$



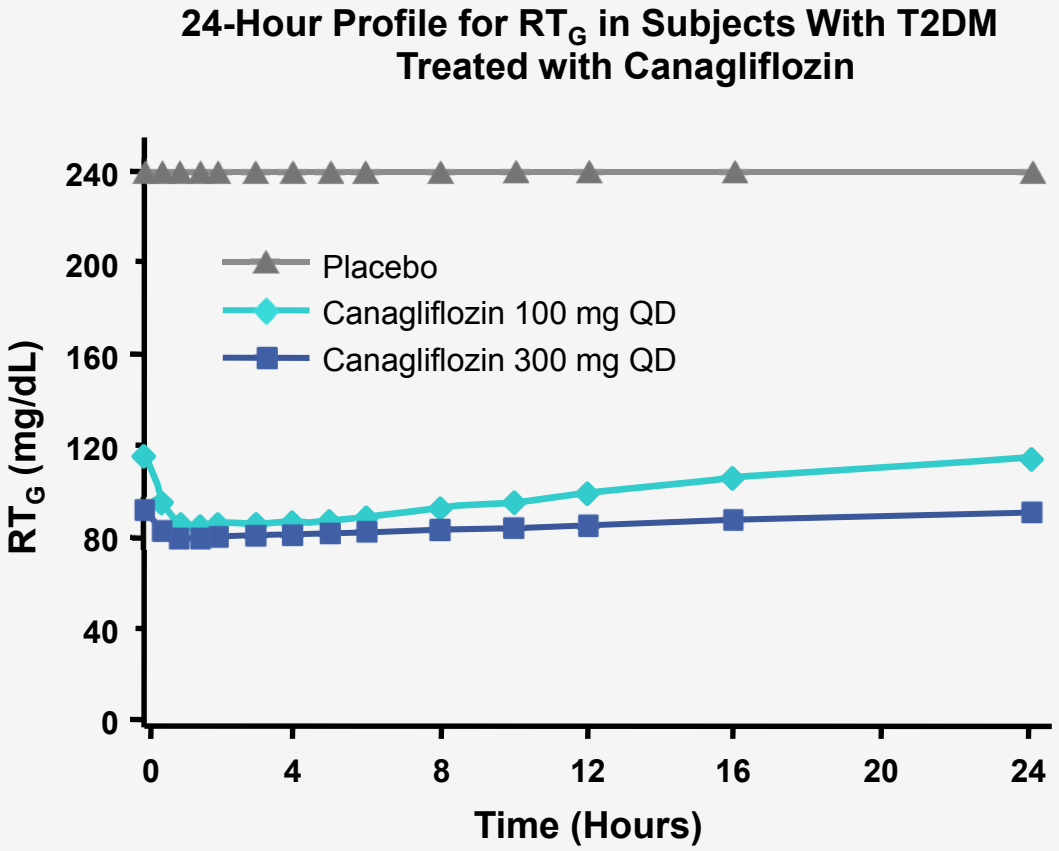

*Renal threshold for glucose

# Canagliflozin: Pharmacokinetics and Pharmacodynamics

## Pharmacokinetics

- Half-life of 11-13 hrs supports once-daily dosing
- Balanced renal and biliary excretion
- Glucuronidation is major metabolic pathway
  - No active metabolites
- No clinically meaningful drug-drug interactions observed

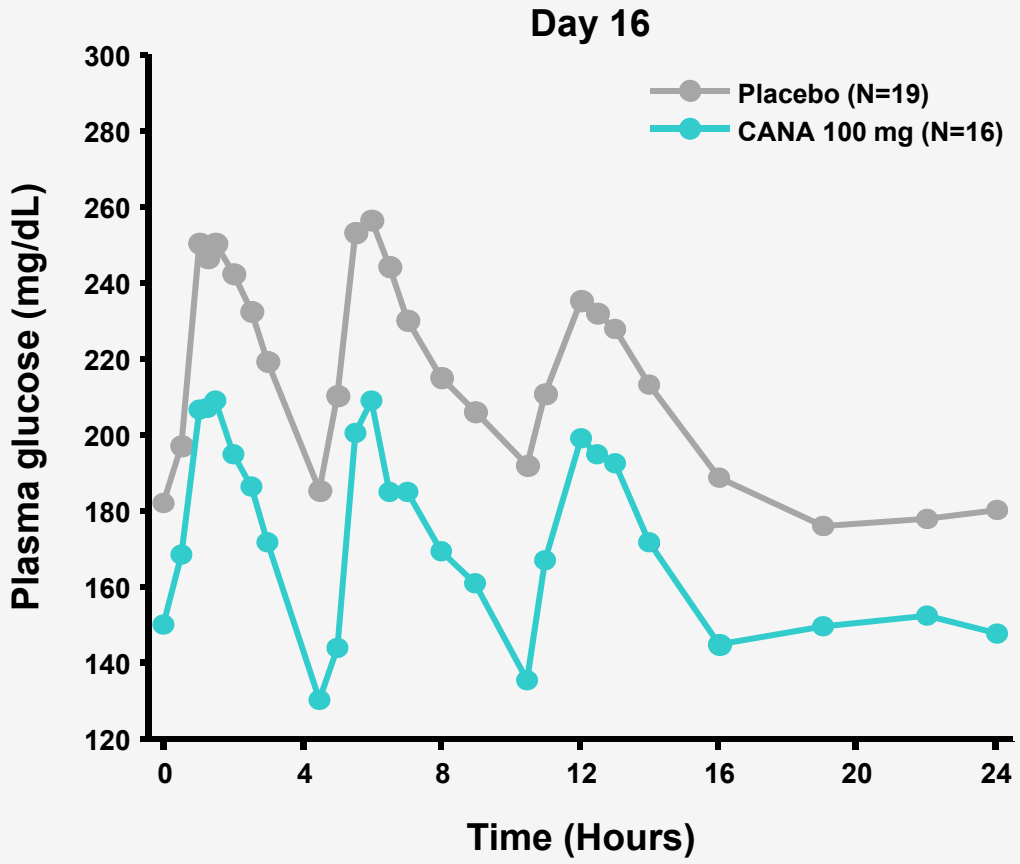
## Pharmacodynamics




Profiles shown were obtained from PK/PD model developed using pooled Phase 1 dataset.(N=242)

# Canagliflozin Treatment Lowers Plasma Glucose Concentrations Throughout the Entire Day

Example: CANA 100 mg treatment in subjects with T2DM



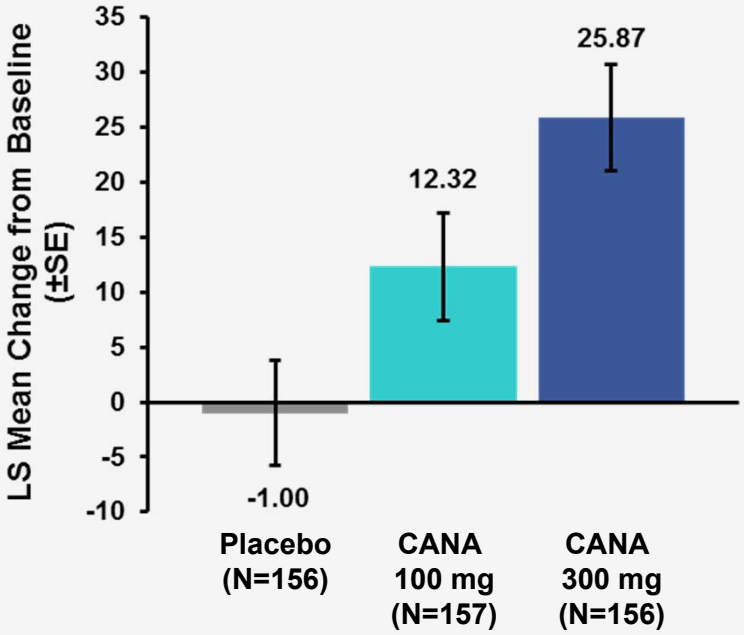

Canagliflozin lowers fasting, postprandial, and 24-h mean plasma glucose

Data shown are mean values from NAP1002

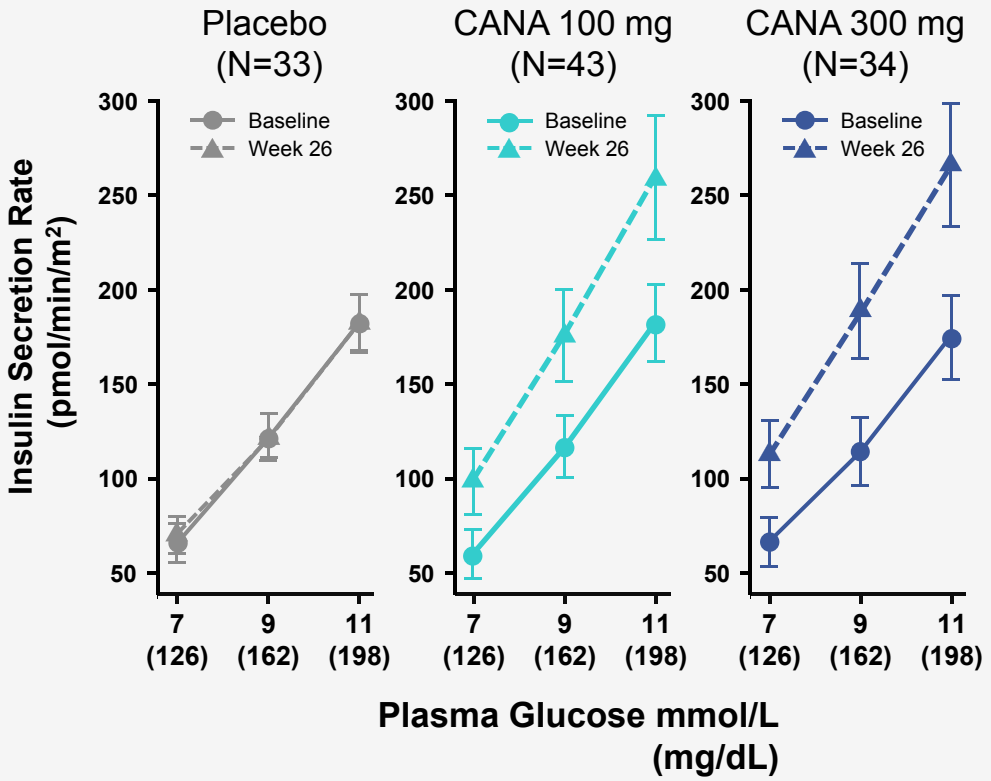
# Canagliflozin Treatment Improves Indices of Beta-cell Function

**Data from DIA3002 (Week 26)**

HOMA2-%B (Fasting-based index)




Insulin Secretion During FS-MMTT




- Similar results observed in all studies in subjects with T2DM where these indices have been assessed
- Effects believed to be secondary to improved glucose control rather than direct effects of SGLT inhibition

Data shown are mean ± s.e.

# Summary of Pharmacodynamic Effects of CANA 100 mg and 300 mg

| Effect | CANA 100 mg | CANA 300 mg |
|---|---|---|
| Increased UGE | + | ++ |
| Maximal $RT_G$ lowering during daytime | + | + |
| Maximal $RT_G$ lowering for full 24 h | | + |
| Reduced fasting and postprandial glucose | + | ++ |
| Delayed intestinal glucose absorption (only after dosing with meal) | | + |
| Improved indices of beta-cell function | + | ++ |

# Phase 3 Program Overview and Efficacy

# Phase 3 Clinical Development Program: 9 Studies Conducted

**Monotherapy** | **Dual Combination** | **Triple Combination** | **Insulin +/- oral(s)**

**Monotherapy (DIA3005)**
26 / 26 wks N=587

**Combo with MET (DIA3006)**
26 / 26 wks N=1284

**Combo with MET/PIO (DIA3012)**
26 / 26 wks N=344

**Combo with INSULIN (Substudy DIA3008)**
18 wks N=1718

**Combo with SU (Substudy DIA3008)**
18 wks N=127

**Combo with MET/SU (DIA3002)**
26 / 26 wks N=469

**Combo with MET vs GLIM (DIA3009)**
52 / 52 wks N=1452

**Combo with MET/SU vs SITA (DIA3015)**
52 wks N=756

Pbo-control

Active-control

## Studies in Special T2DM Populations
Placebo-controlled studies / add-on to current diabetes treatment

**Older Subjects - Bone Safety and Body Comp (DIA3010)**
26 / 78 wks N=716

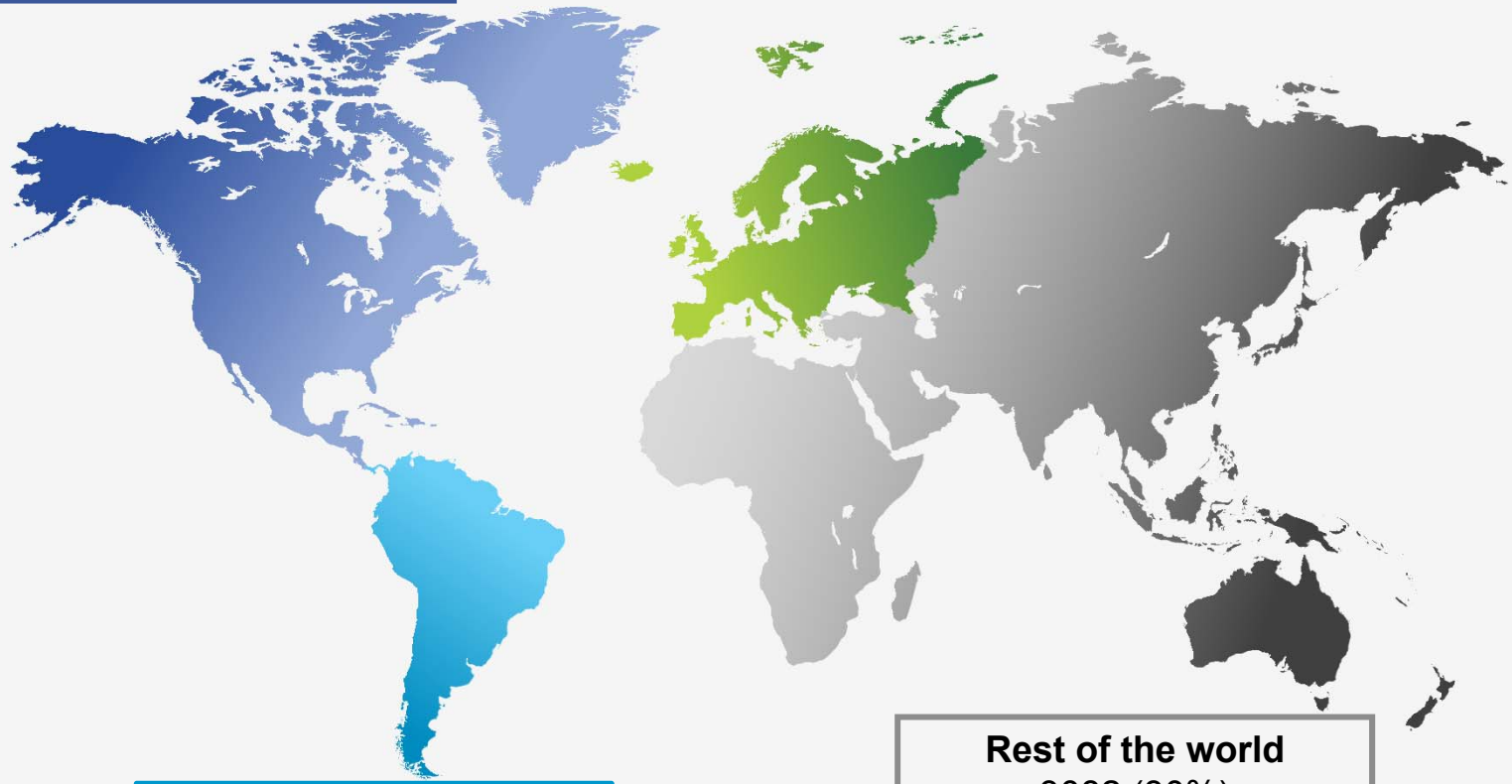
**Renal Impairment (DIA3004)**
26 / 26 wks N=272

**CV Safety Study (DIA3008: CANVAS)**
Event-driven N=4330

# Distribution of Subjects Phase 3

**North America**
**Canada, Mexico, USA**
3743 (36%)

**EU/EEA/EFTA6**
2681 (26%)



**Central/South America**
795 (8%)

**Rest of the world**
3082 (30%)

# Baseline Characteristics – Worldwide and US
## All Randomized Subjects from Phase 3 Studies

| Characteristic | Worldwide N=10301 | US N=2634 |
|---|---|---|
| **Age, y** | | |
| Mean (SD) | 59.5 (9.46) | 58.8 (9.86) |
| **Sex, n (%)** | | |
| Male | 5965 (58) | 1523 (58) |
| Female | 4336 (42) | 1111 (42) |
| **Race, n (%)** | | |
| White | 7411 (72) | 2158 (82) |
| Black or African-American | 452 (4) | 359 (14) |
| Asian | 1643 (16) | 50 (2) |
| Other [a] | 795 (8) | 67 (3) |
| **Ethnicity, n (%)** | | |
| Hispanic or Latino | 1699 (16) | 444 (17) |
| Not Hispanic or Latino | 8563 (83) | 2177 (83) |
| Not provided | 39 (<1) | 13 (<1) |

[a] Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, and Other

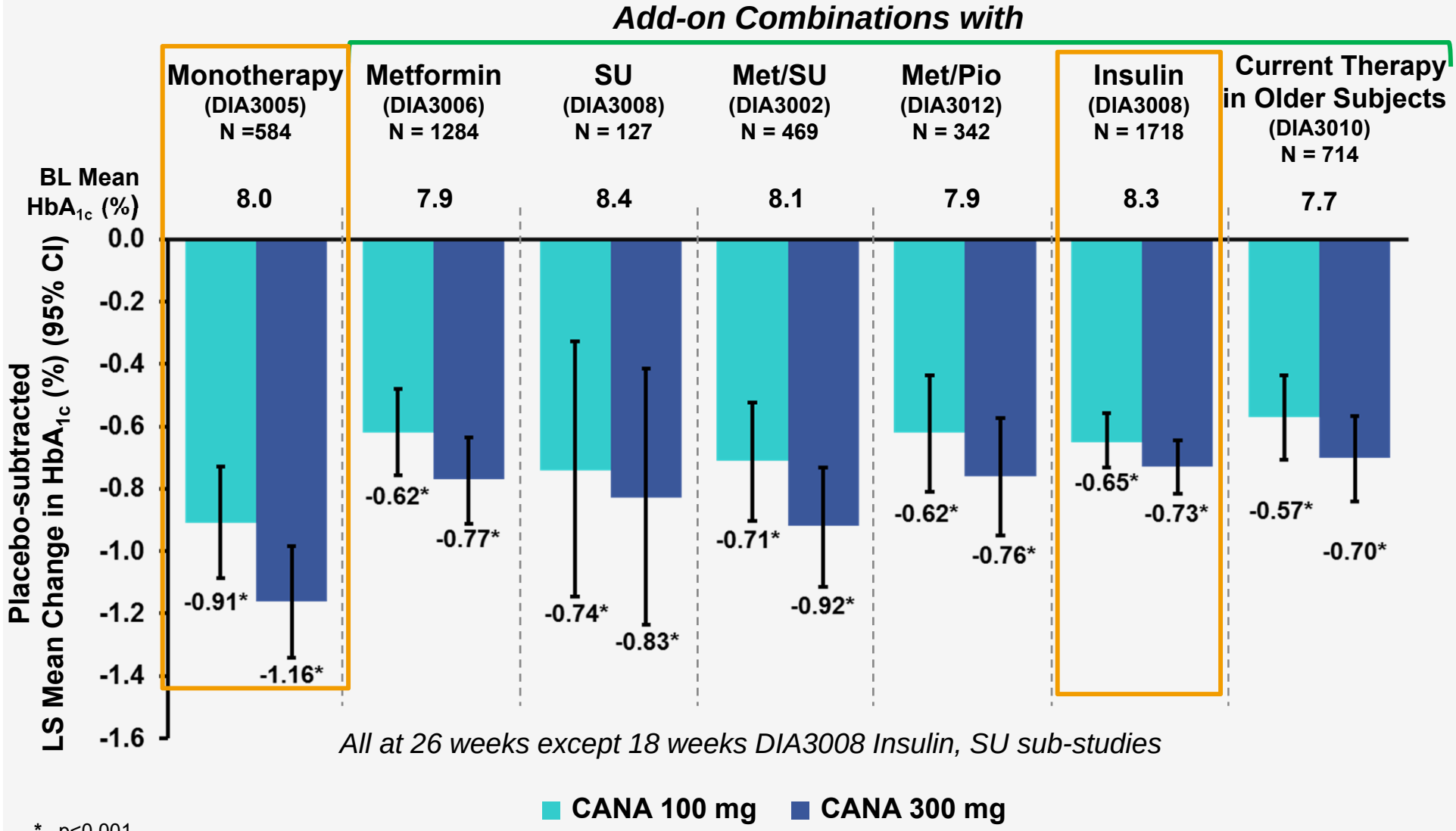
# Overview of Efficacy

- Results from Placebo-controlled Studies
- Results from Active-controlled Studies
- Results in Subjects with Renal Impairment (Stage 3 CKD)
- $HbA_{1c}$ Subgroup Analyses

# Placebo-controlled Studies

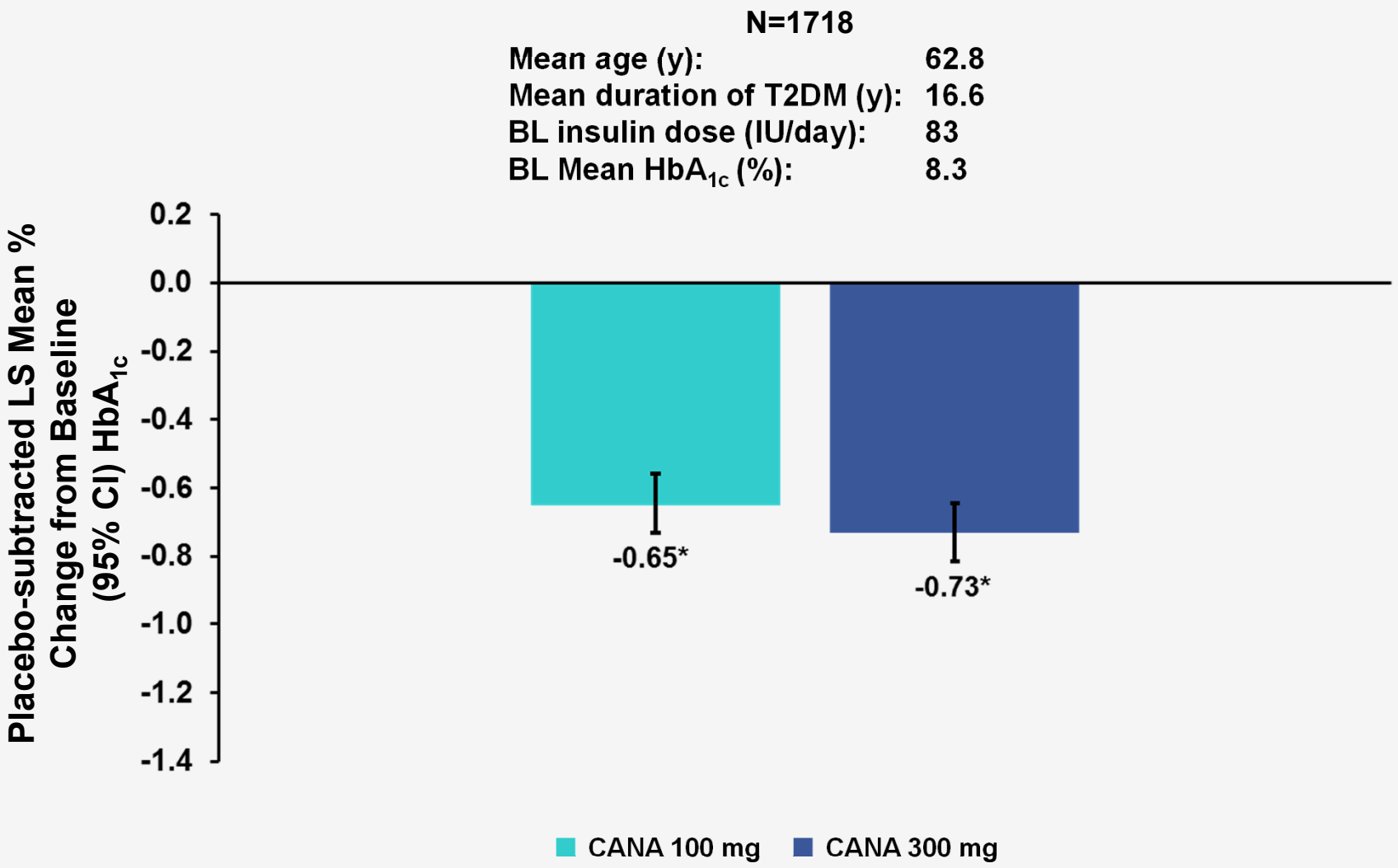
- $HbA_{1c}$
- Body weight
- Systolic blood pressure

# $HbA_{1c}$ Change from Baseline
## Placebo-controlled Phase 3 Studies



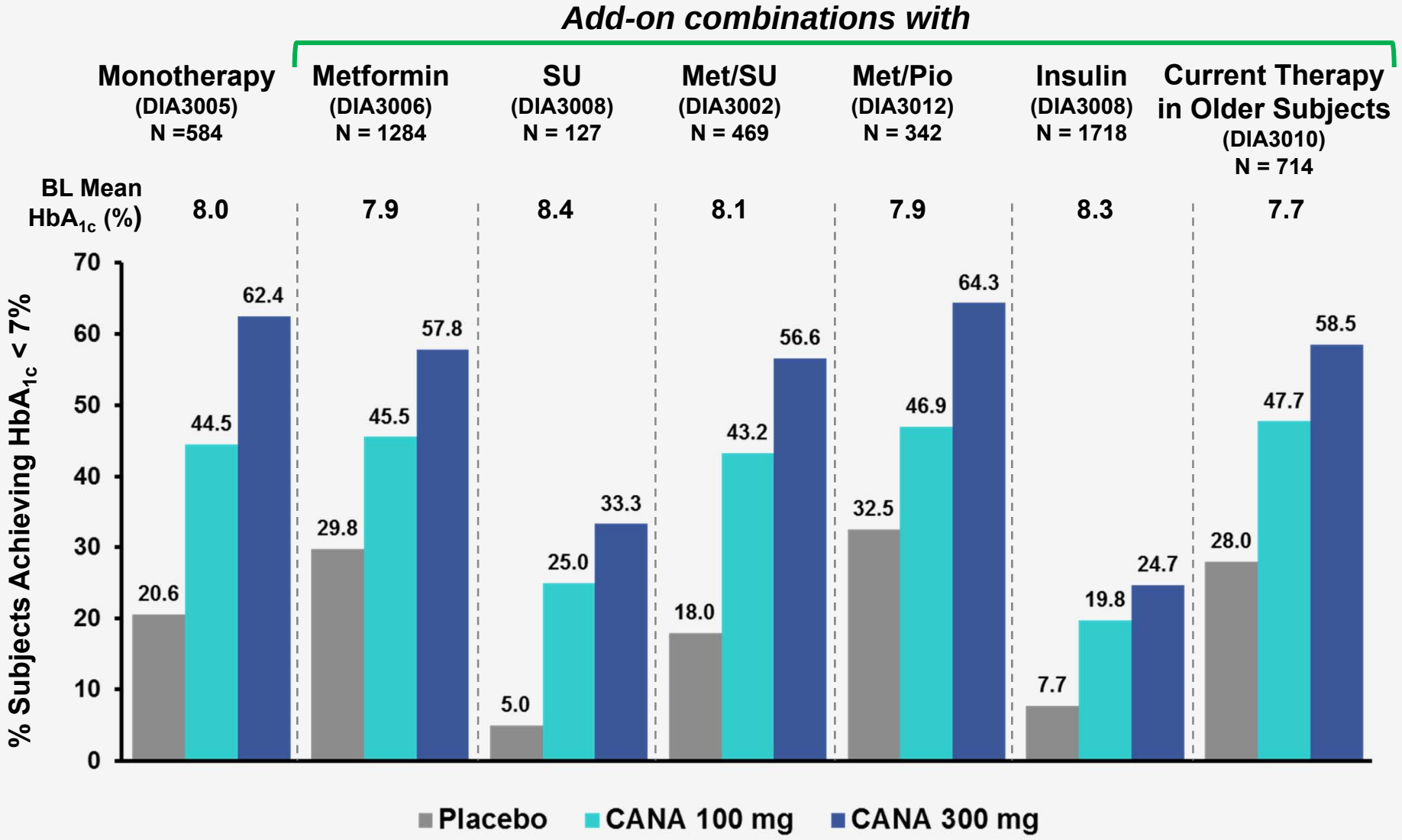

* p<0.001
Based on ANCOVA models, data prior to rescue (LOCF)

# $HbA_{1c}$ Change from Baseline at Week 18
## Placebo-controlled Add-on to Insulin Substudy (DIA3008 Insulin)



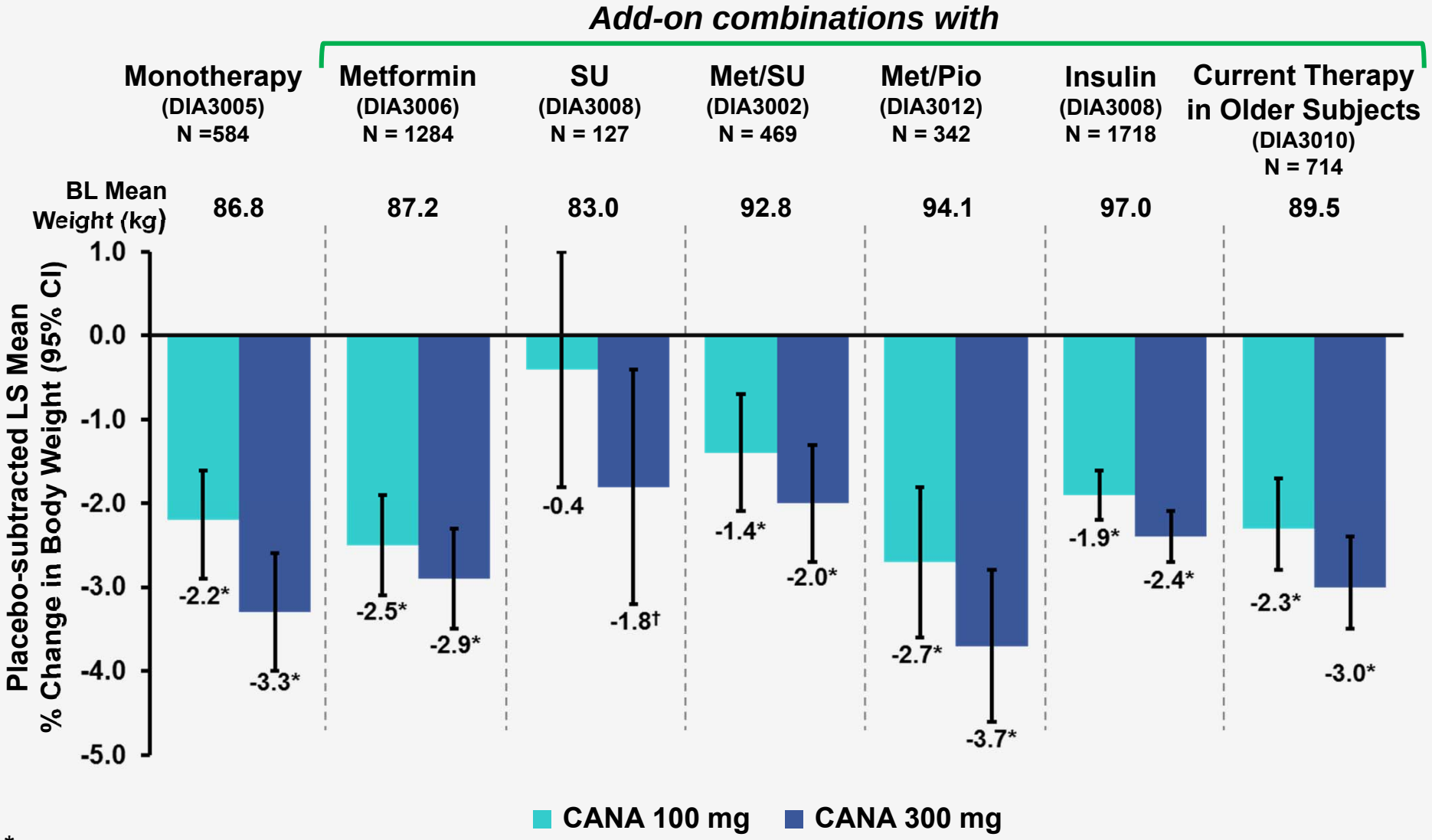

* p <0.001
Based on ANCOVA model, data prior to rescue (LOCF)

# Subjects with $HbA_{1c}$ <7% at Primary Endpoint
## Placebo-controlled Phase 3 Studies



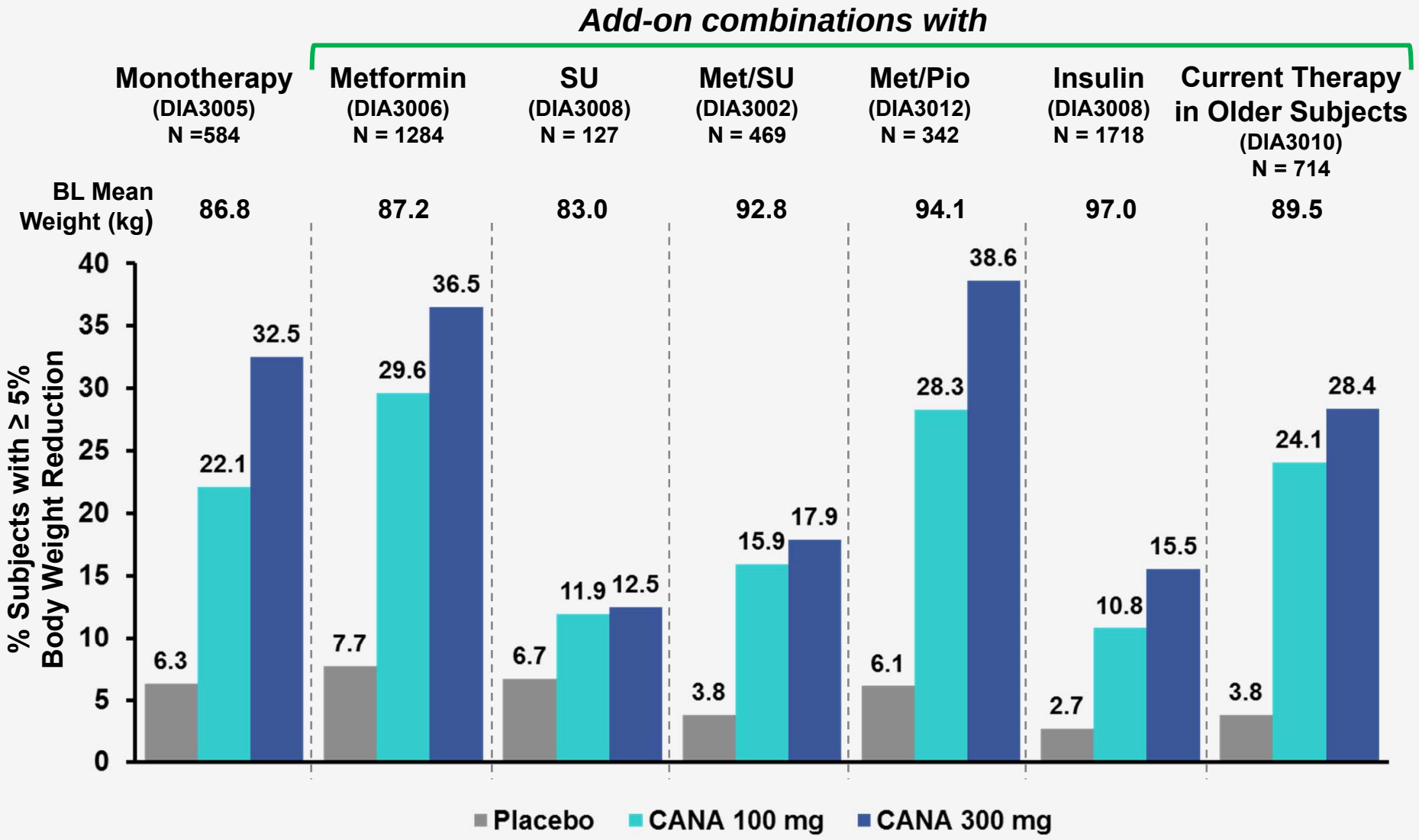

Data prior to rescue (LOCF);

# Body Weight Percent Change from Baseline
## Placebo-controlled Phase 3 Studies



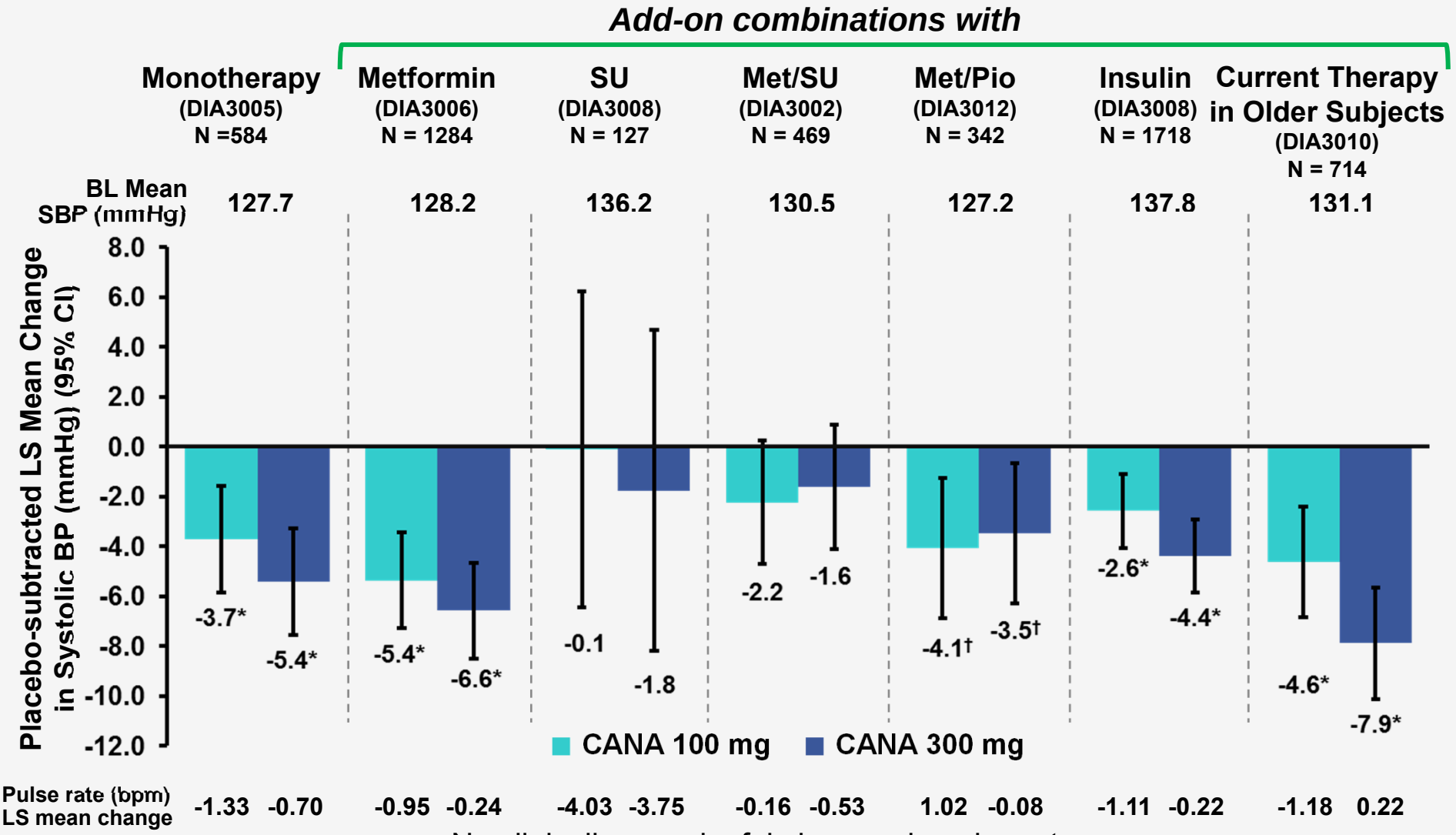

* p <0.001; † p <0.05
Based on ANCOVA models, data prior to rescue (LOCF)

# Percent of Subjects with Weight Reduction ≥5%
## Placebo-controlled Phase 3 Studies




Data prior to rescue (LOCF)

# Systolic Blood Pressure Change from Baseline
## Placebo-controlled Phase 3 Studies



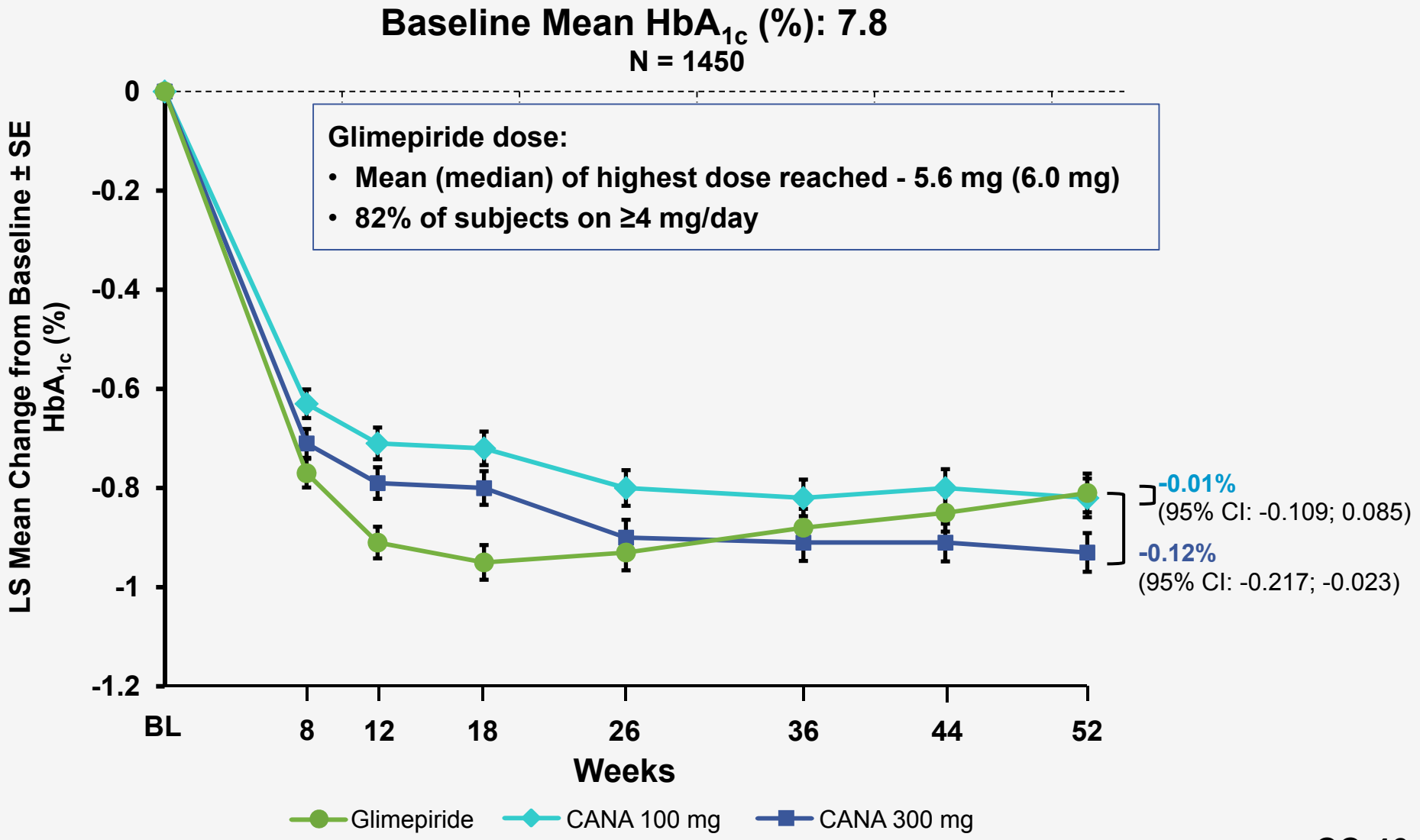

No clinically meaningful changes in pulse rate

* p<0.001; ** p<0.05
Based on ANCOVA models, data prior to rescue (LOCF)

# Results from Active-controlled Studies

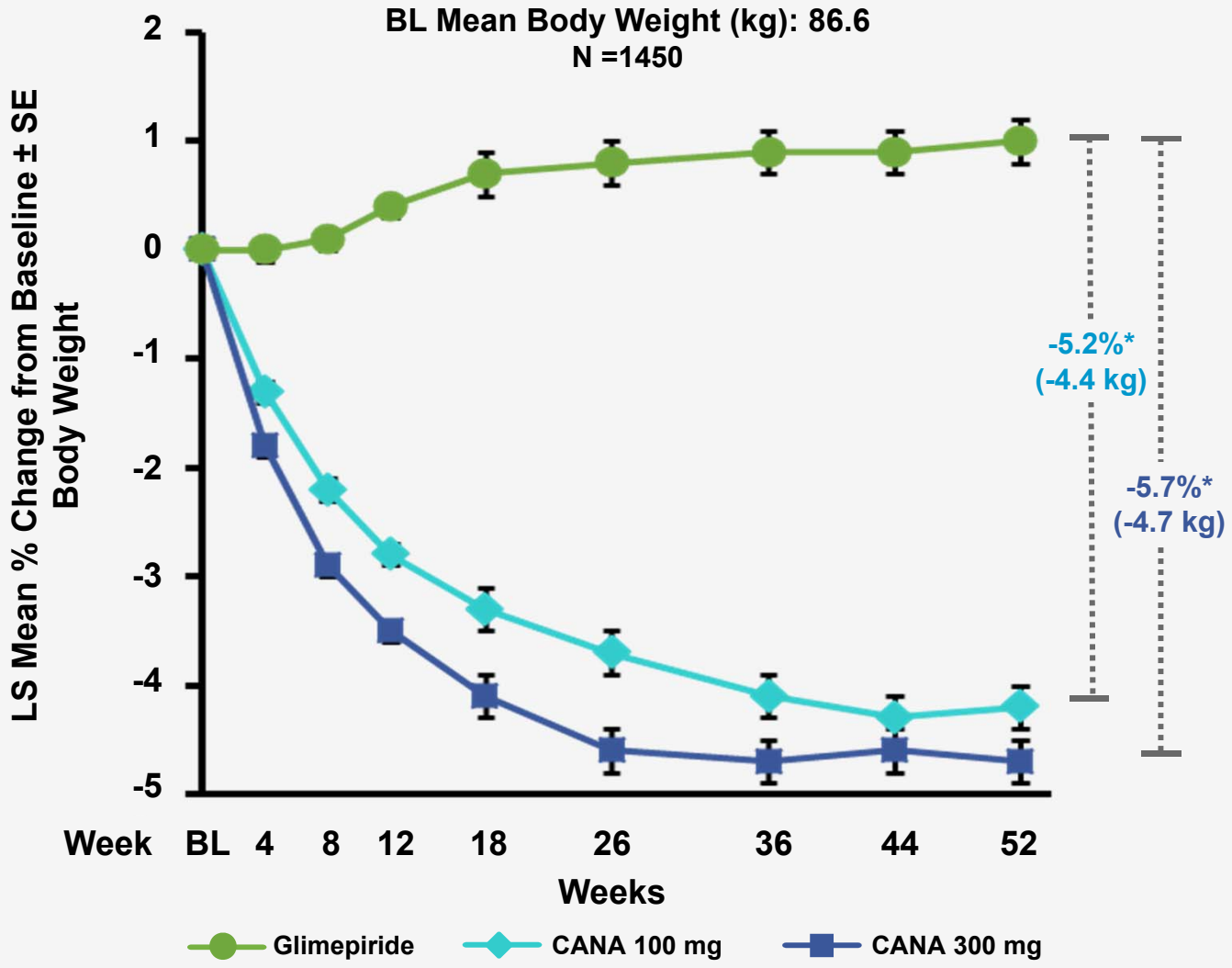
- $HbA_{1c}$
- Body weight
- Systolic blood pressure

# HbA1c Change from Baseline Over Time
## Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)




Based on ANCOVA model, data prior to rescue (LOCF)

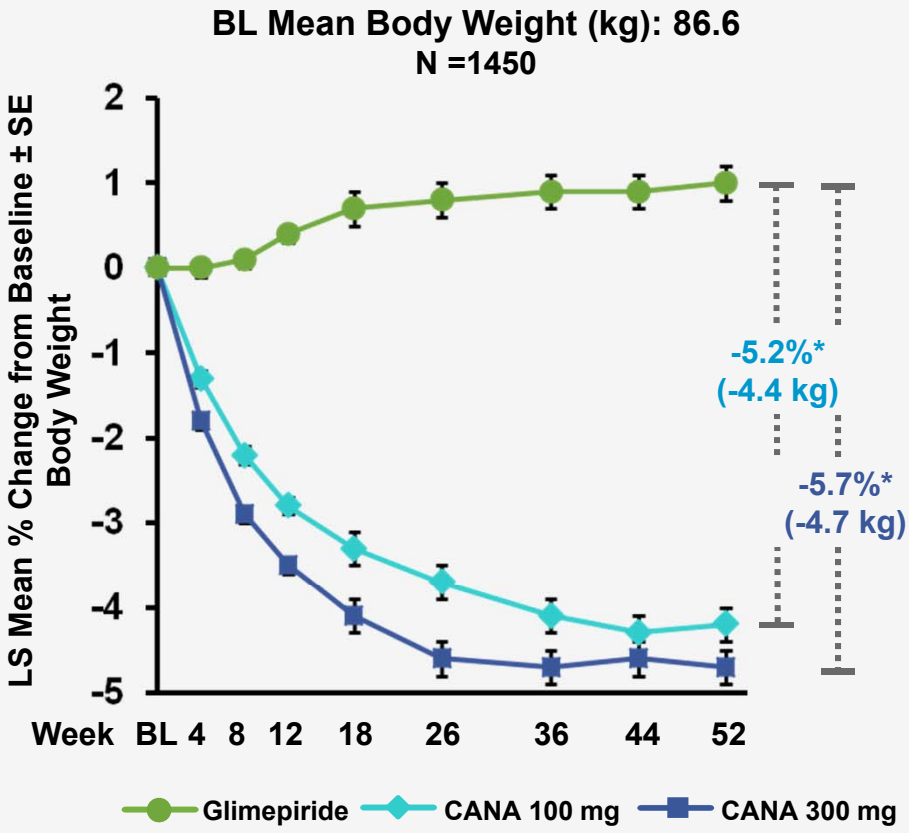
# Body Weight Percent Change from Baseline Over Time
## Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)



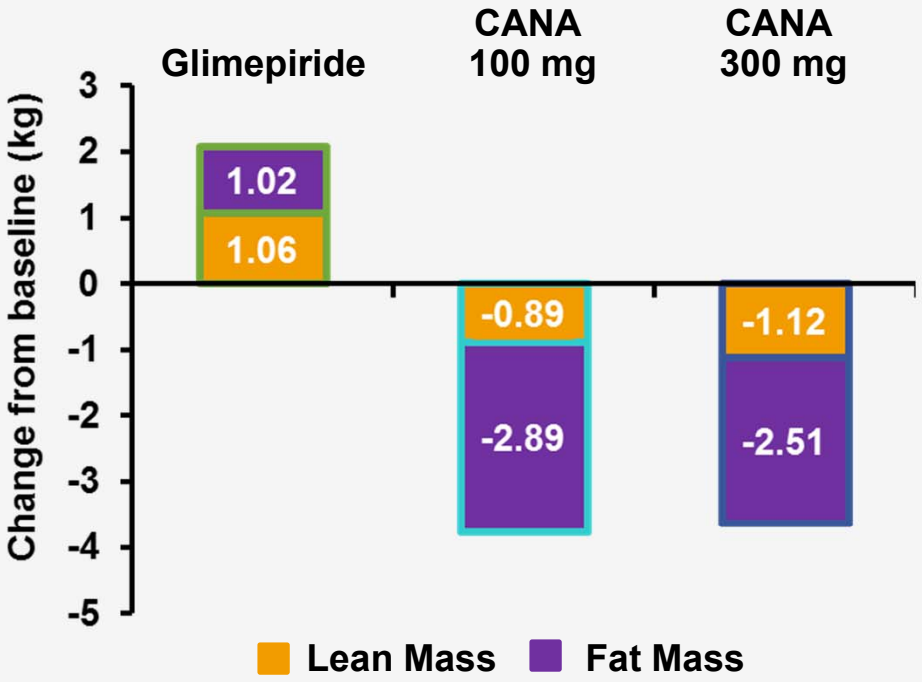

* p <0.001
Based on ANCOVA model, data prior to rescue (LOCF)

# Changes in Body Composition and Weight
## Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)

### Weight Loss Over Time



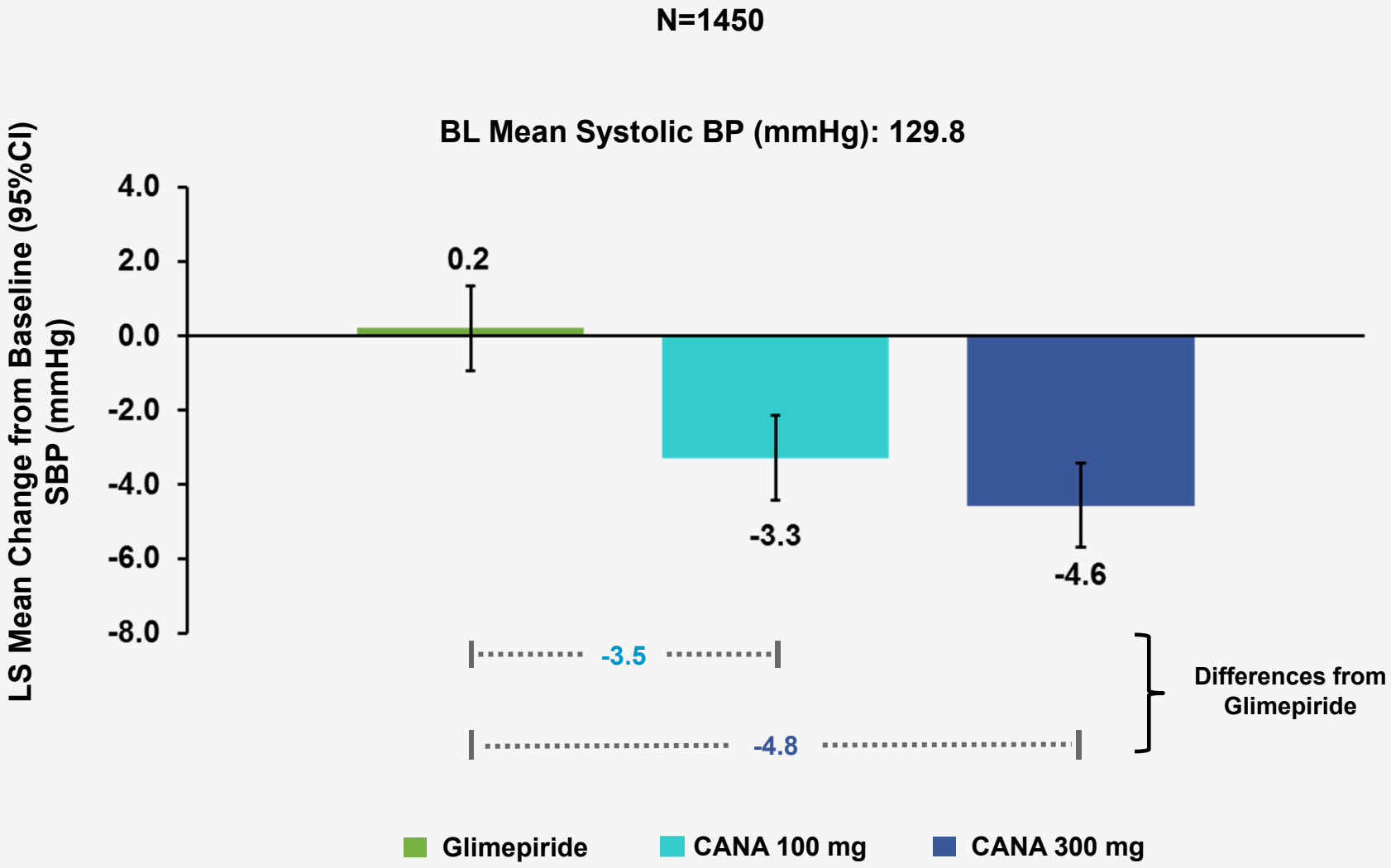

### Change in Body Composition (DXA Analysis Subgroup) N=312




Weight changes relative to glimepiride in DXA analysis subgroup (-5.3 kg and -5.0 kg for CANA 100 mg and 300 mg, respectively) were similar to overall cohort.

* p <0.001
Based on ANCOVA model, data prior to rescue (LOCF)

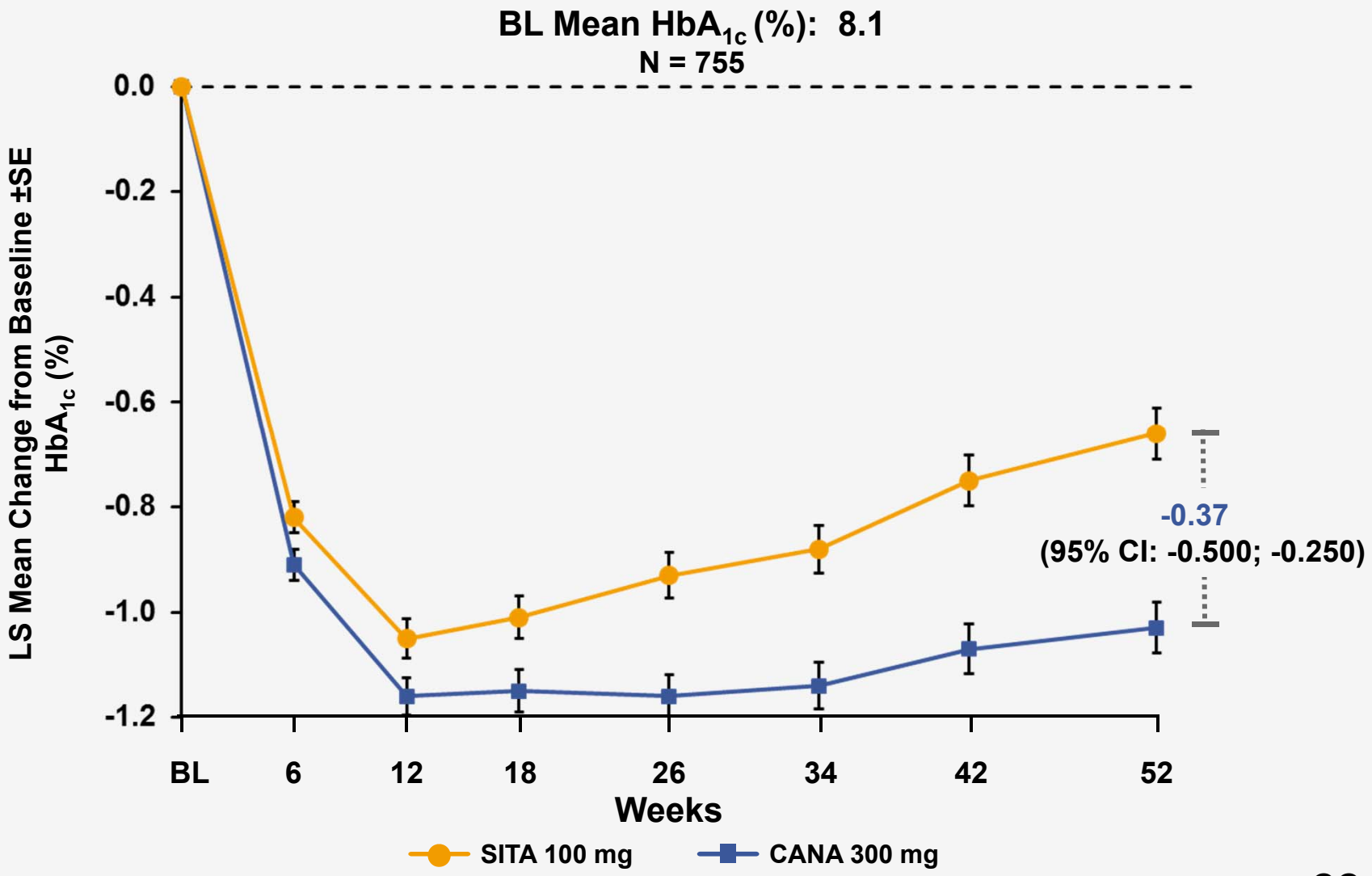
# Systolic Blood Pressure Change From Baseline at Week 52
## Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)




SBP endpoint was not included in the prespecified testing sequence, however CI excluded 0.
Based on ANCOVA model, data prior to rescue (LOCF)

# $HbA_{1c}$ Change from Baseline Over Time

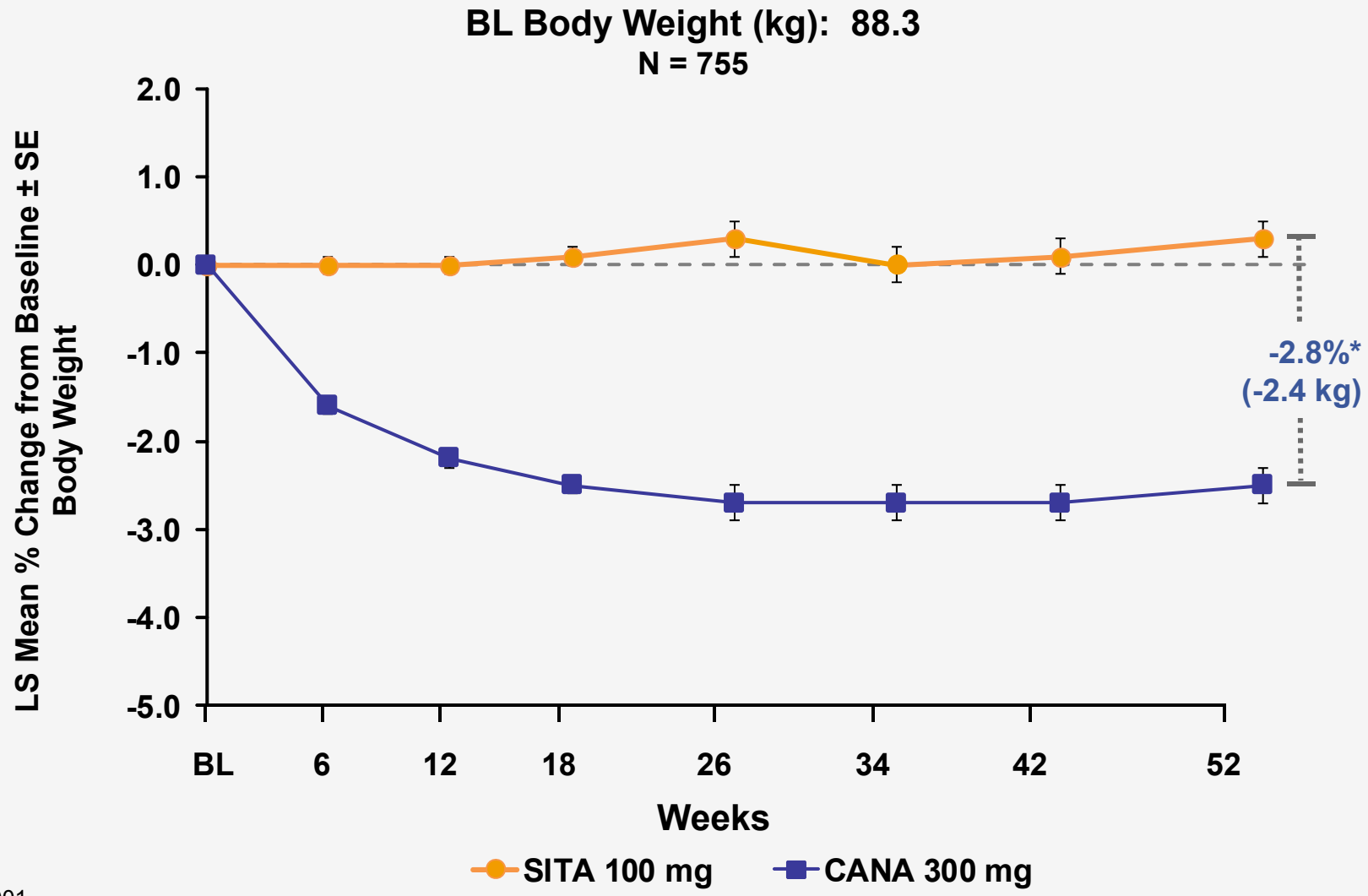
## Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)




Based on ANCOVA model (LOCF)

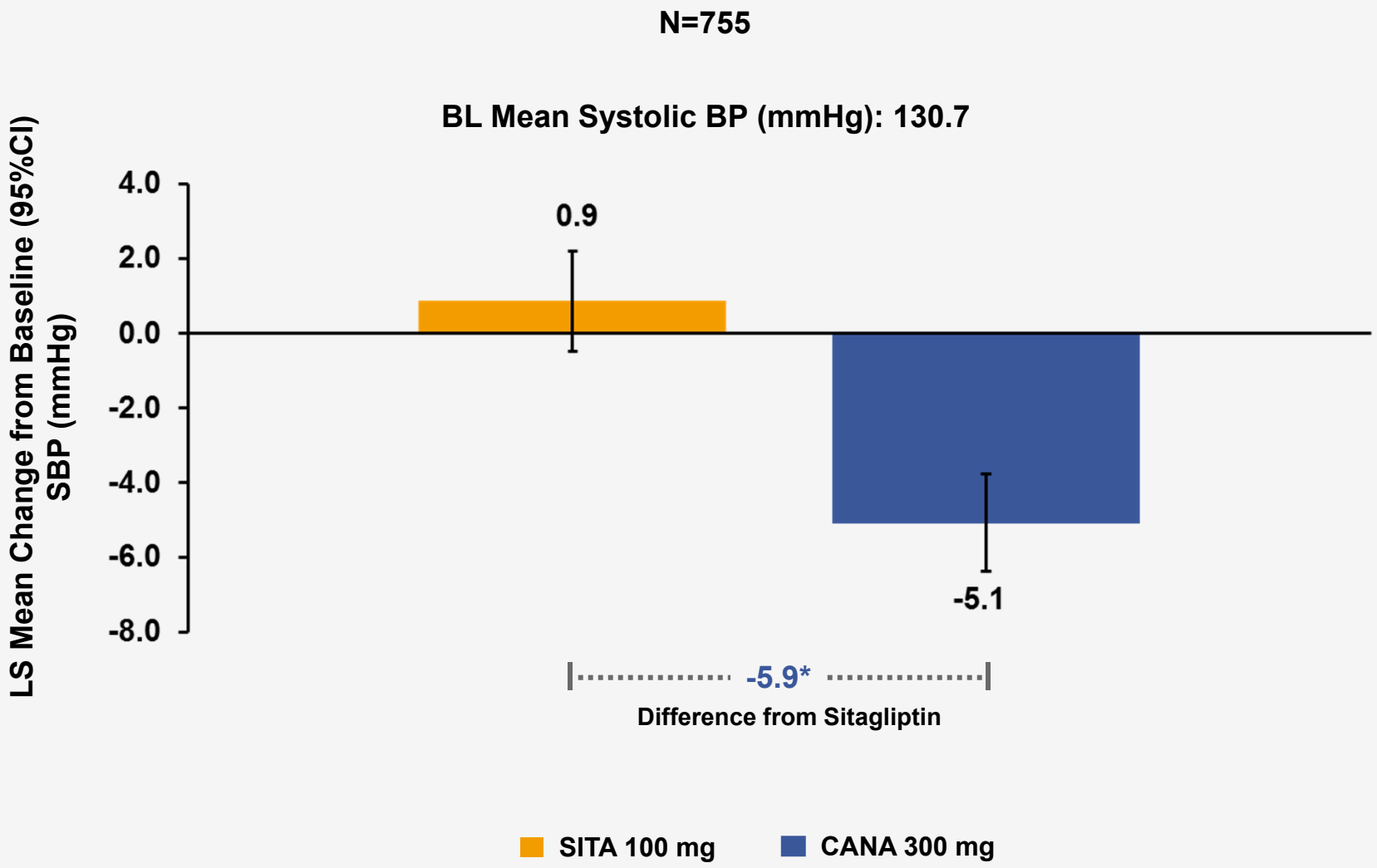
# Body Weight Percent Change from Baseline Over Time

## Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)




*p < 0.001
Based on ANCOVA model (LOCF)

# Systolic Blood Pressure Change From Baseline at Week 52
## Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)

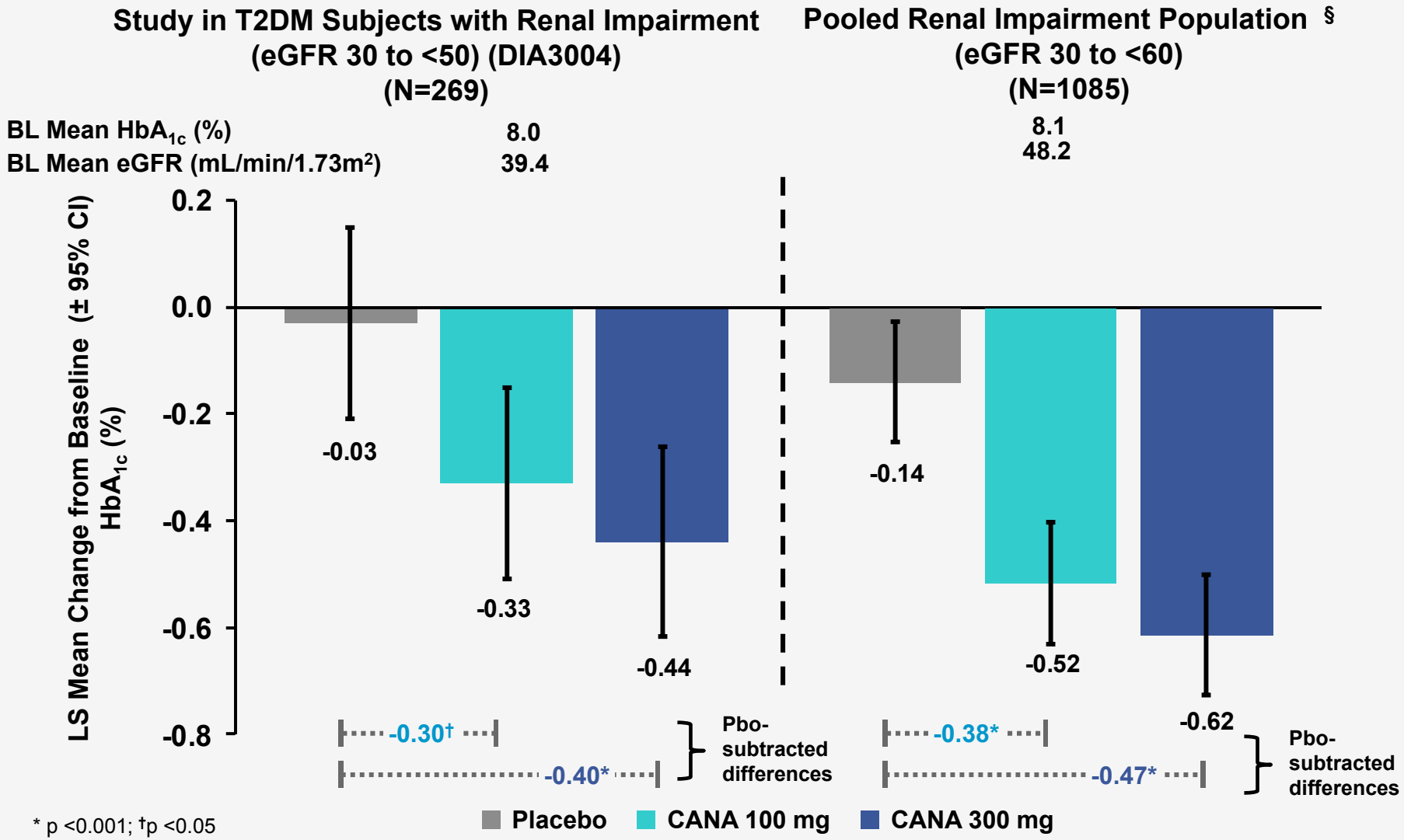



* p <0.001
Based on ANCOVA model (LOCF)

# Results in Subjects with Renal Impairment

- HbA1c
- Body weight
- Systolic blood pressure

# $HbA_{1c}$ Change from Baseline
## Renal Impairment Study (DIA3004) and Pooled Population (DS2)



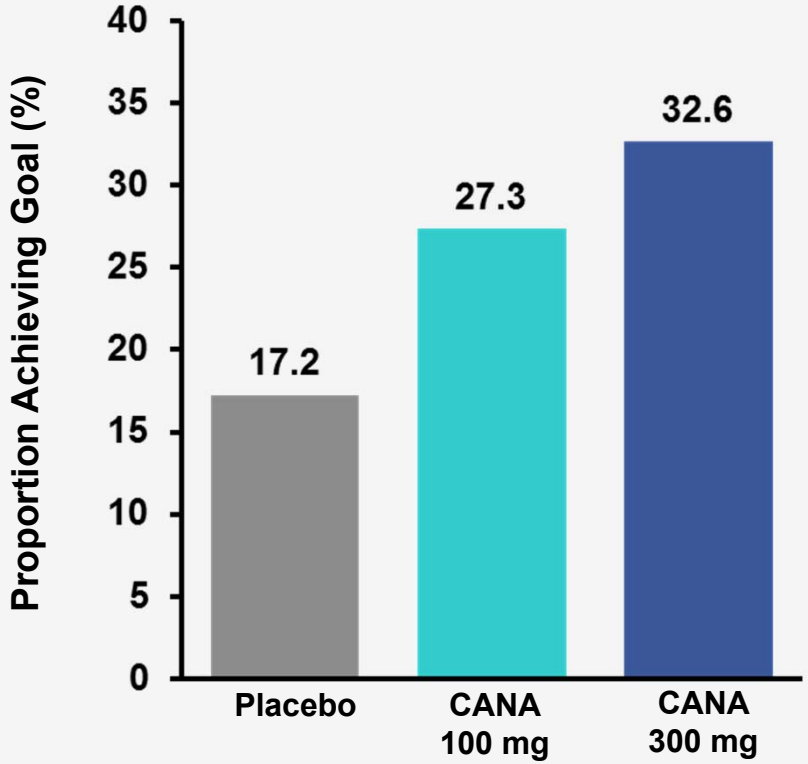

* p <0.001; †p <0.05

§Data from monotherapy study (DIA3005), renal impairment study (DIA3004), study in older subjects (DIA3010), and CV study (DIA3008)

# Subjects Achieving $HbA_{1c}$ <7.0%
## Renal Impairment Study (DIA3004) and Pooled Population (DS2)

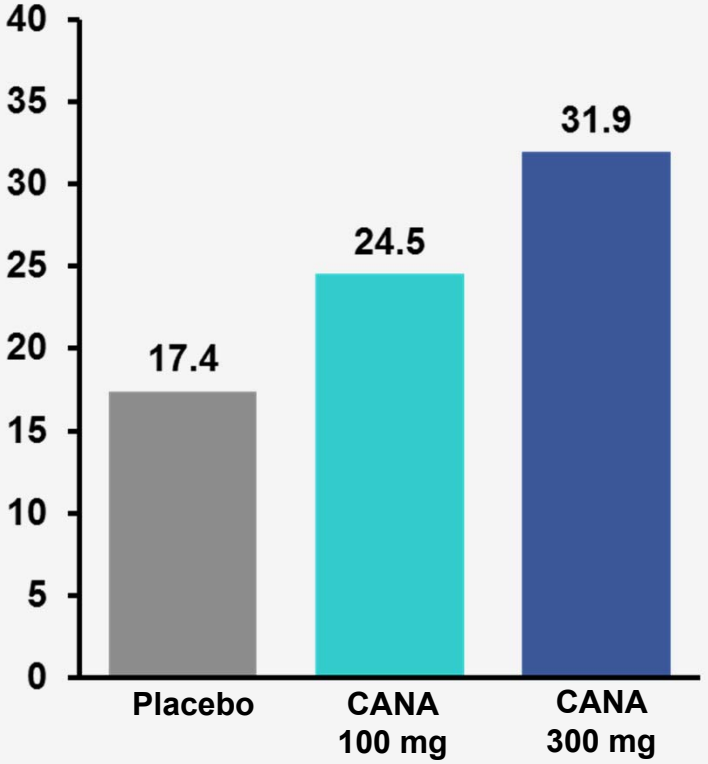
### DIA3004 (eGFR* 30 to <50)

BL Mean $HbA_{1c}$ 8.0%
N = 269



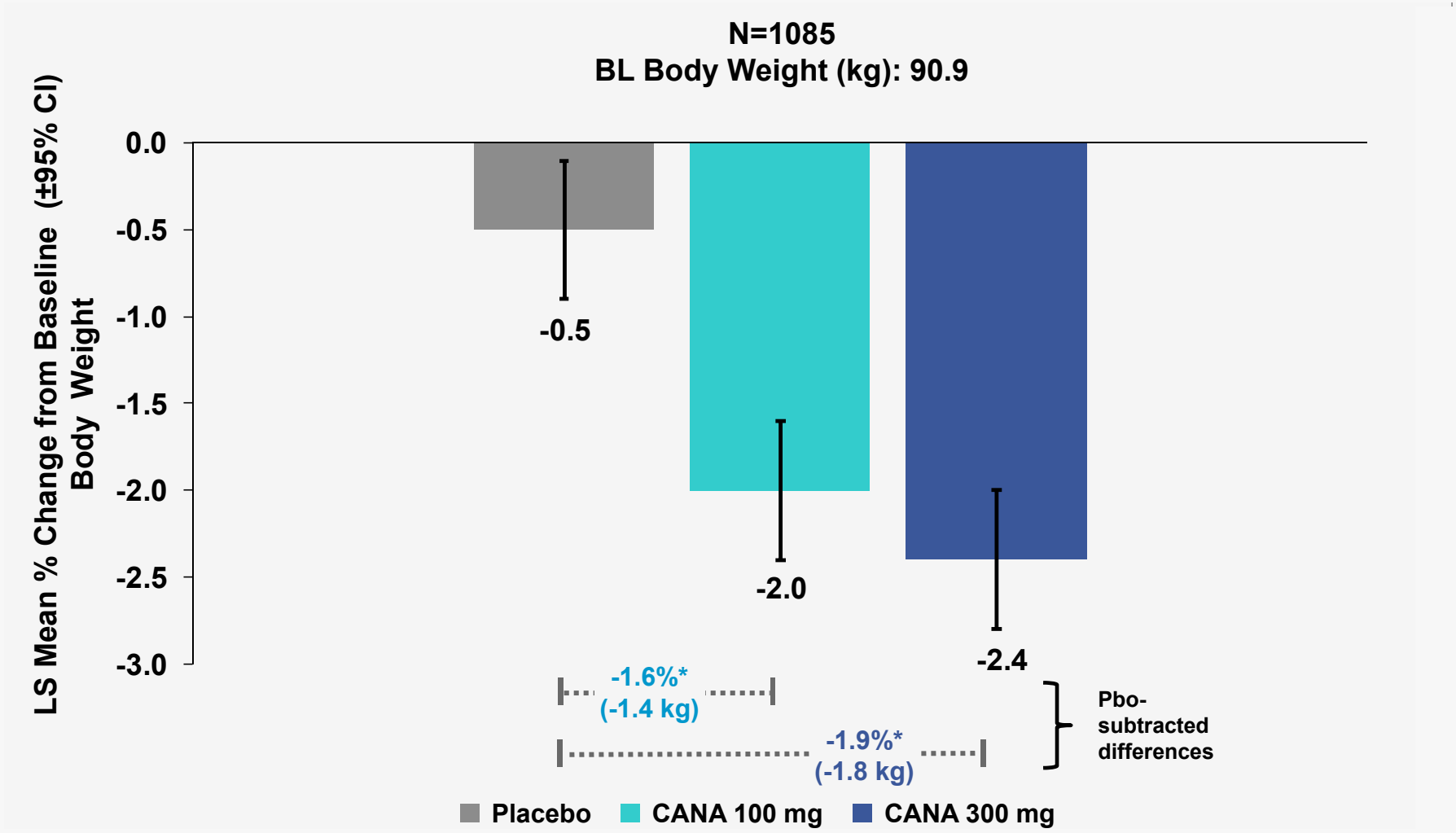

### Pooled Renal Impairment Population (eGFR* 30 to <60)

BL Mean $HbA_{1c}$ 8.1%
N = 1085



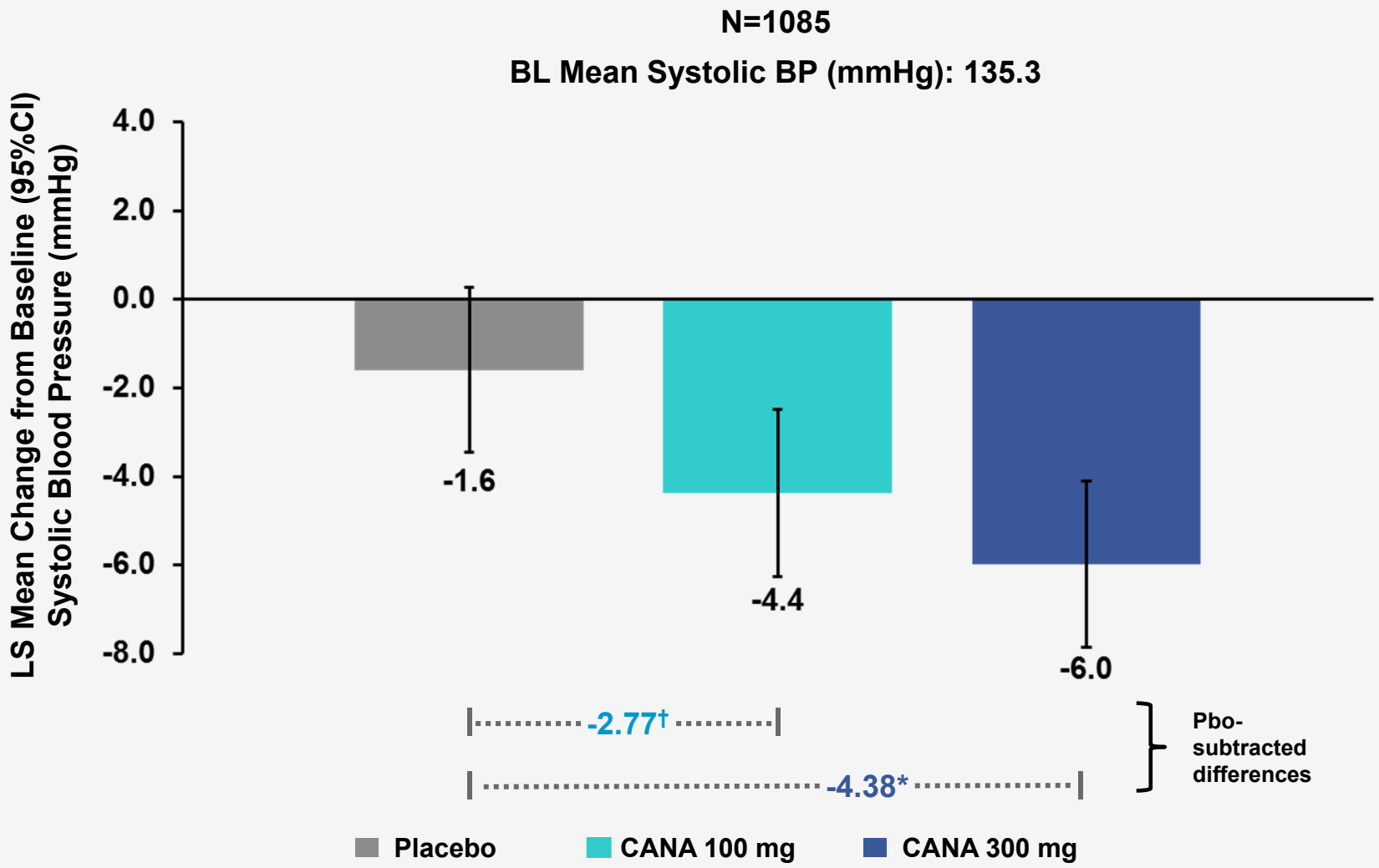

*mL/min/1.73m²

# Body Weight Percent Change from Baseline at Endpoint
## Pooled Renal Impairment Population (eGFR 30 to <60)




* p <0.001
Based on ANCOVA model, data prior to rescue (LOCF)

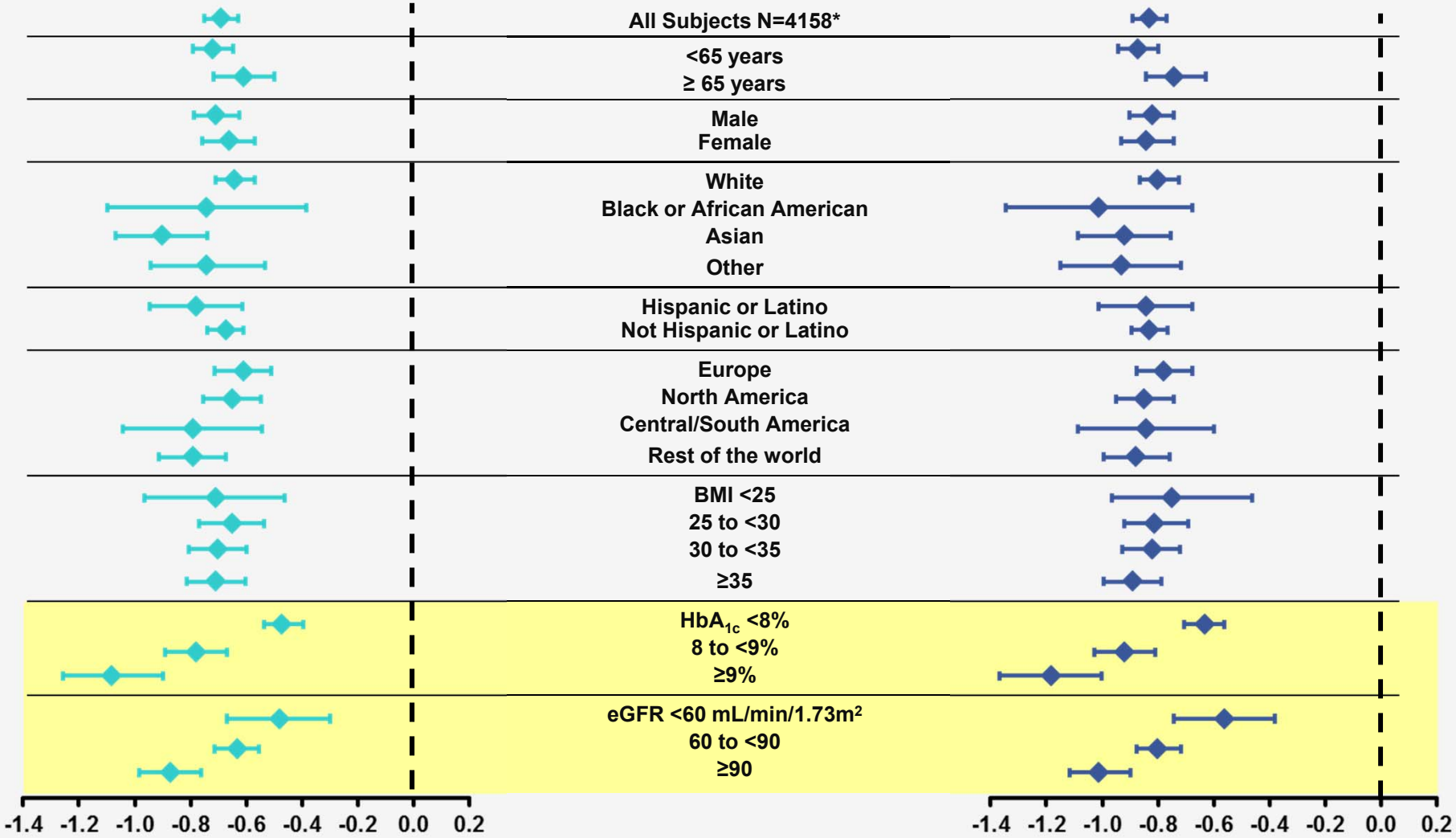
# Systolic BP Change from Baseline at Endpoint
## Pooled Renal Impairment Population (eGFR 30 to <60)




* p <0.001; † p <0.05
Based on ANCOVA model, data prior to rescue (LOCF)

# $HbA_{1c}$ Subgroup Analyses

# $HbA_{1c}$ Change from Baseline by Subgroup Factors
## Pooled Placebo-controlled Studies for Efficacy




*includes: monotherapy, dual therapy, triple therapy, and insulin

# Summary of Canagliflozin Efficacy Data

- HbA1c
  - Consistent improvement across Phase 3 studies, with more subjects achieving HbA1c goal
  - Sustained response over 52 weeks
  - Meaningful, albeit lesser, reductions in HbA1c in subjects with renal impairment
- Other efficacy parameters
  - Consistent reductions in body weight
  - Consistent reductions in systolic blood pressure
- Additional efficacy with 300 mg relative to 100 mg

# Overview of Safety and Tolerability

**Peter Stein, MD**
Head of Development, Metabolism
Janssen Research and Development, LLC

# Agenda

- Pooled datasets for safety: definition, characteristics, exposure
  - Placebo-controlled 26 week studies dataset
  - “Broad Dataset”
- Review of adverse drug reactions (ADRs)
  - Overview of identified ADRs
  - Review of specific ADRs: UTIs, related to reduced intravascular volume
- Additional safety assessments
  - LDL-C changes and CV meta-analysis (including events in 1st 30 days in CANVAS)
  - Renal safety and safety in stage 3 CKD subjects
  - Bone

# Phase 3 Clinical Development Program: 9 Studies Conducted

**Monotherapy** | **Dual Combination** | **Triple Combination** | **Insulin +/- oral(s)**

**Monotherapy**
(DIA3005)
26 / 26 wks N=587

**Combo with MET**
(DIA3006)
26 / 26 wks N=1284

**Combo with MET/PIO**
(DIA3012)
26 / 26 wks N=344

**Combo with INSULIN**
(Substudy DIA3008)
18 wks N=1784

**Combo with SU**
(Substudy DIA3008)
18 wks N=127

**Combo with MET/SU** (DIA3002)
26 / 26 wks N=469

**Combo with MET vs GLIM**
(DIA3009)
52 / 52 wks N=1452

**Combo with MET/SU vs SITA**
(DIA3015)
52 wks N=756

Pbo-control
Active-control

## Studies in Special T2DM Populations
Placebo-controlled studies / add-on to current diabetes treatment

**Older Subjects - Bone Safety and Body Comp**
(DIA3010)
26 / 78 wks N=716

**Renal Impairment**
(DIA3004)
26 / 26 wks N=272

**CV Safety Study**
(DIA3008: CANVAS)
Event-driven N=4330

# Phase 3 Pooled Safety Populations:
## Placebo-controlled Studies Dataset (DS1)


**Monotherapy**
**(DIA3005)**
**26 / 26 wks N=587**

**Combo with MET**
**(DIA3006)**
**26 / 26 wks N=1284**

**Combo with MET/PIO**
**(DIA3012)**
**26 / 26 wks N=344**

**Combo with MET/SU**
**(DIA3002)**
**26 / 26 wks N=469**

***4 Phase 3 studies / 2313 subjects***
***26 week double-blind duration***

# Phase 3 Pooled Safety Populations:
## Broad Dataset (DS3)

**Monotherapy** | **Dual Combination** | **Triple Combination** | **Insulin +/- oral(s)**

**Monotherapy**
(DIA3005)
26 / 26 wks N=587

**Combo with MET**
(DIA3006)
26 / 26 wks N=1284

**Combo with MET/PIO**
(DIA3012)
26 / 26 wks N=344

**Combo with INSULIN**
(Substudy DIA3008)
18 wks N=1784

**Combo with SU**
(Substudy DIA3008)
18 wks N=127

**Combo with MET/SU** (DIA3002)
26 / 26 wks N=469

**Combo with MET vs GLIM**
(DIA3009)
52 / 52 wks N=1452

Pbo-control
Active-control

***8 Phase 3 Studies***
***9439 subjects***
•PBO/comparators pooled
(="Non-CANA" group)

## Studies in Special T2DM Populations
Placebo-controlled studies / add-on to current diabetes treatment

**Older Subjects - Bone Safety and Body Comp**
(DIA3010)
26 / 78 wks N=716

**Renal Impairment**
(DIA3004)
26 / 26 wks N=272

**CV Safety Study**
(DIA3008: CANVAS)
Event-driven N=4330

# Baseline Characteristics
## Pooled Datasets

| | Placebo-controlled Studies Dataset N=2313 | Broad Dataset N=9439 | CANVAS N=4,327 |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Male | 49.5 | 58.2 | 66.1 |
| Female | 50.5 | 41.8 | 33.9 |
| **Age (y), Mean (SD)** | 56.0 (9.81) | 59.9 (9.35) | 62.4 (8.02) |
| **Race, n (%)** | | | |
| White | 72.2 | 72.6 | 73.4 |
| Black or African-American | 5.1 | 3.8 | 2.4 |
| Asian | 12.3 | 15.8 | 18.4 |
| Other | 10.4 | 7.8 | 5.8 |
| **Body mass index, kg/m$^2$,Mean (SD)** | 32.1 (6.42) | 31.9 (6.06) | 32.1 (6.24) |
| **$HbA_{1c}$ (%), Mean (SD)** | 8.0 (0.93) | 8.0 (0.90) | 8.2 (0.92) |
| **Duration of diabetes (y), Mean (SD)** | 7.3 (6.04) | 10.6 (7.53) | 13.4 (7.52) |
| **eGFR, Mean** | 88 | 81 | 77 |
| **≥ 1 Microvascular Complications (%)** | 18.9 | 33.1 | 44.2 |

# Exposure

## Placebo-controlled Studies Dataset and Broad Dataset through 01 Jul 2012

| | Placebo-controlled Studies Dataset | | | Broad Dataset through 01 Jul 2012 | | |
|---|---|---|---|---|---|---|
| | Placebo N=646 | CANA 100 mg N=833 | CANA 300 mg N=834 | Non-CANA N=3262 | CANA 100 mg N=3092 | CANA 300 mg N=3085 |
| **Category, %** | | | | | | |
| ≥ 50 weeks | 0 | 0 | 0 | 77.7 | 83.5 | 81.9 |
| ≥ 76 weeks | 0 | 0 | 0 | 40.6 | 46.4 | 45.2 |
| **Mean (SD)** | 23.8 (5.9) | 24.2 (5.7) | 24.3 (5.5) | 64.4 (30.2) | 68.8 (29.0) | 67.4 (30.2) |
| **Median** | 26.0 | 26.1 | 26.1 | 65.9 | 72.9 | 72.4 |
| **Total Exposure (subject-years)** | 294 | 387 | 388 | 4024 | 4075 | 3987 |

Note: Total duration = Treatment duration = last dose date - first dose date + 1 (in days).

*Broad dataset does not include DIA3015*

# Summary of Adverse Events
## Broad Dataset through 01 Jul 2012

| | Non-CANA N=3262 % | CANA 100 mg N=3092 % | CANA 300 mg N=3085 % |
|---|---|---|---|
| Any adverse events | 75.8 | 76.6 | 77.0 |
| AEs leading to discontinuation | 5.0 | 5.6 | 7.3 |
| Serious AEs | 13.6 | 13.5 | 13.2 |
| Serious AEs leading to discontinuation | 2.2 | 2.0 | 1.7 |
| Deaths | 1.1 | 0.8 | 0.8 |

- Genital mycotic infections: male and female
- Osmotic diuresis-related (pollakiuria, thirst)
- Other: UTI, renal-related

# Adverse Drug Reactions

- Overview of ADRs
- Discussion of specific ADRs:
  - Urinary tract infections
  - Reduced intravascular volume-related AEs

# Summary of Adverse Drug Reactions
## ≥ 2% and > Placebo in the Placebo-controlled Studies Dataset

| | Placebo N=646 n (%) | CANA 100 mg N=833 n (%) | CANA 300 mg N=834 n (%) |
|---|---|---|---|
| **Gastrointestinal Disorders** | | | |
| Constipation | 6 (0.9) | 15 (1.8) | 19 (2.3) |
| Thirst | 1 (0.2) | 23 (2.8) | 19 (2.3) |
| **Renal and Urinary Disorders** | | | |
| Polyuria or pollakiuria | 5 (0.8) | 44 (5.3) | 38 (4.6) |
| Urinary tract infection | 26 (4.0) | 49 (5.9) | 36 (4.3) |
| **Reproductive System and Breast Disorders** | | | |
| Balanitis or balanoposthitis | 2 (0.6) | 17 (4.2) | 15 (3.7) |
| Vulvovaginal candidiasis | 10 (3.2) | 44 (10.4) | 49 (11.4) |

# Additional ADRs Identified

In *Broad Dataset*

- Reduced intravascular volume-related AEs (eg, postural dizziness)
- Less common (< 2%): rash/urticaria

In *individual* Phase 3 studies

- Hypoglycemia in patients on insulin or sulphonylurea agent
  - Low rate of hypoglycemia in studies of subjects not on agents associated with hypoglycemia

# Adverse Drug Reactions

**Urinary tract infections**

**Adverse events related to reduced intravascular volume**

# Incidence of Urinary Tract Infection Adverse Events
## Broad Dataset through 01 Jul 2012

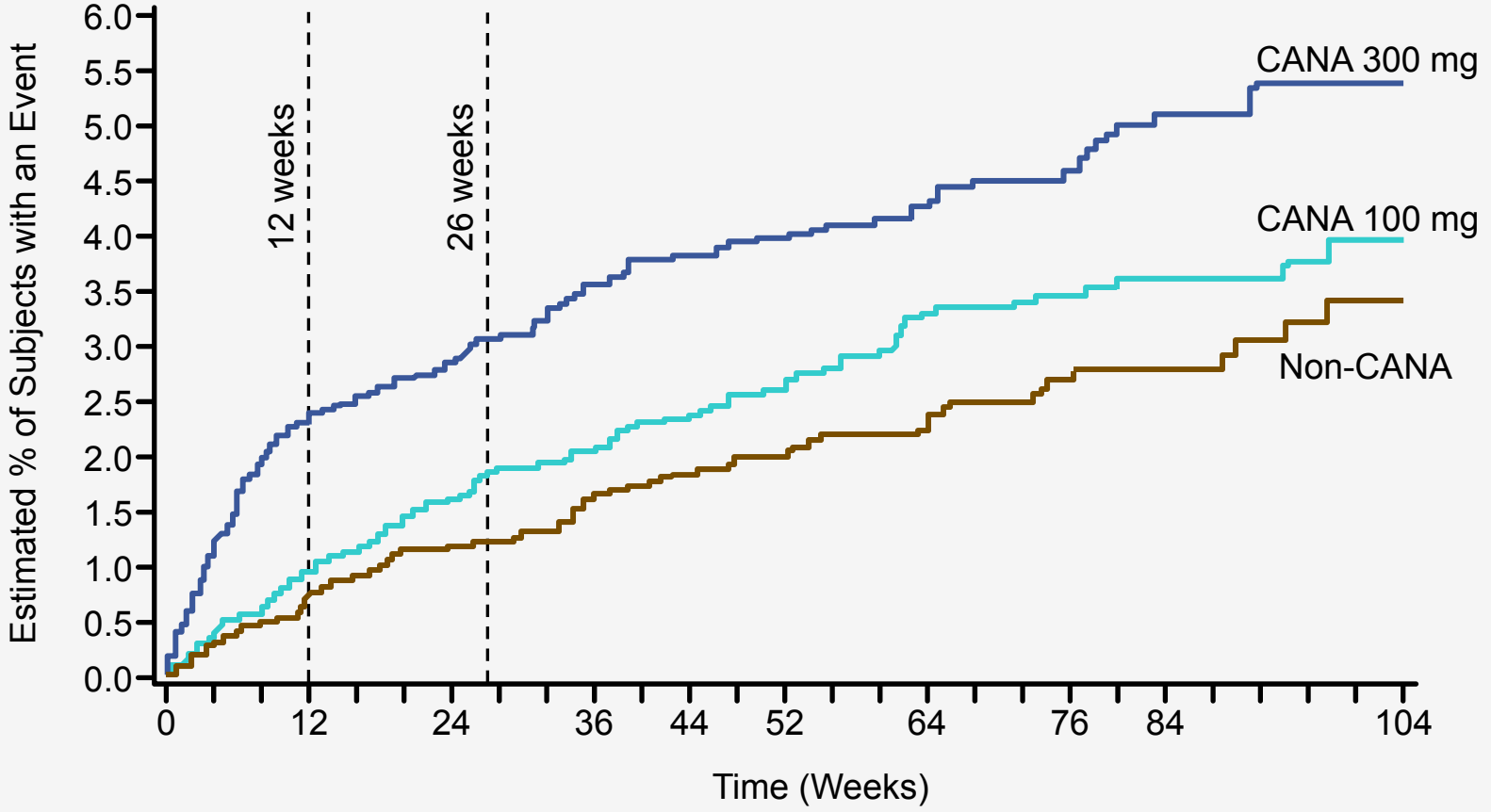
| | Non-CANA N=3262 n (%) | CANA 100 mg N=3092 n (%) | CANA 300 mg N=3085 n (%) | All CANA N=6177 n (%) |
|---|---|---|---|---|
| Any adverse events | 218 (6.7) | 254 (8.2) | 250 (8.1) | 504 (8.2) |
| Upper UTI AE | 11 (0.3) | 20 (0.6) | 10 (0.3) | 30 (0.5) |
| AEs leading to discontinuation | 4 (0.1) | 11 (0.4) | 6 (0.2) | 17 (0.3) |
| Serious AEs | 12 (0.4) | 16 (0.5) | 8 (0.3) | 24 (0.4) |

# Reduced Intravascular Volume-Related AEs
## Broad Dataset through 01 Jul 2012

| | Non-CANA N=3262 n (%) | CANA 100 mg N=3092 n (%) | CANA 300 mg N=3085 n (%) |
|---|---|---|---|
| Any adverse events | 78 (2.4) | 99 (3.2) | 141 (4.6) |
| AEs leading to discontinuation | 4 (0.1) | 2 (0.1) | 3 (0.1) |
| Serious AEs | 11 (0.3) | 12 (0.4) | 8 (0.3) |
| | | | |
| Specific AE Terms | | | |
| *Blood pressure decreased* | 1 (<0.1) | 2 (0.1) | 2 (0.1) |
| *Dehydration* | 13 (0.4) | 6 (0.2) | 13 (0.4) |
| *Dizziness postural* | 24 (0.7) | 26 (0.8) | 33 (1.1) |
| *Hypotension* | 20 (0.6) | 47 (1.5) | 60 (1.9) |
| *Orthostatic hypotension* | 6 (0.2) | 8 (0.3) | 27 (0.9) |
| *Orthostatic intolerance* | 1 (<0.1) | 1 (<0.1) | 1 (<0.1) |
| *Presyncope* | 9 (0.3) | 4 (0.1) | 3 (0.1) |
| *Syncope* | 13 (0.4) | 12 (0.4) | 20 (0.6) |
| *Urine output decreased* | 1 (<0.1) | 0 | 0 |

# Time to Event: Reduced Intravascular Volume AE
## Broad Dataset through 01 Jul 2012

*KM estimate*




| Subjects at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Non CANA | 3262 | 3097 | 2861 | 2679 | 2580 | 2506 | 1639 | 1303 | 995 | 344 |
| CANA 100 mg | 3092 | 2954 | 2791 | 2666 | 2582 | 2532 | 1750 | 1395 | 1060 | 369 |
| CANA 300 mg | 3085 | 2866 | 2692 | 2564 | 2491 | 2442 | 1671 | 1345 | 1014 | 370 |

# Risk Factors: Reduced Intravascular Volume AEs
## Broad Dataset Core Period

| | Non-CANA % (n/N) | CANA 100 mg % (n/N) | CANA 300 mg % (n/N) |
|---|---|---|---|
| eGFR (mL/min/1.73m$^2$) | | | |
| <60 | 2.8 (12/436) | 5.0 (19/382) | **8.1 (33/405)** |
| 60 to <90 | 1.5 (26/1788) | 2.4 (40/1686) | 2.9 (48/1680) |
| ≥90 | 1.2 (12/1035) | 1.3 (13/1021) | 2.4 (24/999) |
| Age (years) | | | |
| <75 | 1.5 (46/3107) | 2.2 (64/2929) | 3.1 (90/2913) |
| ≥75 | 2.6 (4/155) | 4.9 (8/163) | **8.7 (15/172)** |
| Use of loop diuretics | | | |
| No | 1.2 (37/3006) | 2.3 (65/2876) | 2.9 (83/2835) |
| Yes | 5.1 (13/256) | 3.2 (7/216) | **8.8 (22/250)** |
| Age <75, not on loop diuretics and with eGFR ≥60 mL/min/1.73m$^2$ | 1.1 (29/2604) | 1.8 (45/2491) | 2.2 (54/2434) |

# Summary: Reduced Intravascular Volume Related Adverse Events

- Dose-related increase in events
  - No increase in AEs leading to discontinuation or SAEs
  - Generally mild-moderate in intensity, short duration
  - Manageable, often with adjustment in concomitant BP-lowering regimen
- Risk factors for dose-related increase identified
  - eGFR < 60 mL/min/1.73 $m^2$, age ≥ 75 yrs, on loop diuretics
  - Supports dosing recommendations to initiate therapy at 100 mg in patients with any 1 of 3 risk factors

# Additional Key Safety Assessments

- CV Meta-analysis Results
- Renal Safety Evaluations
- Bone Safety

# Additional Key Safety Assessments

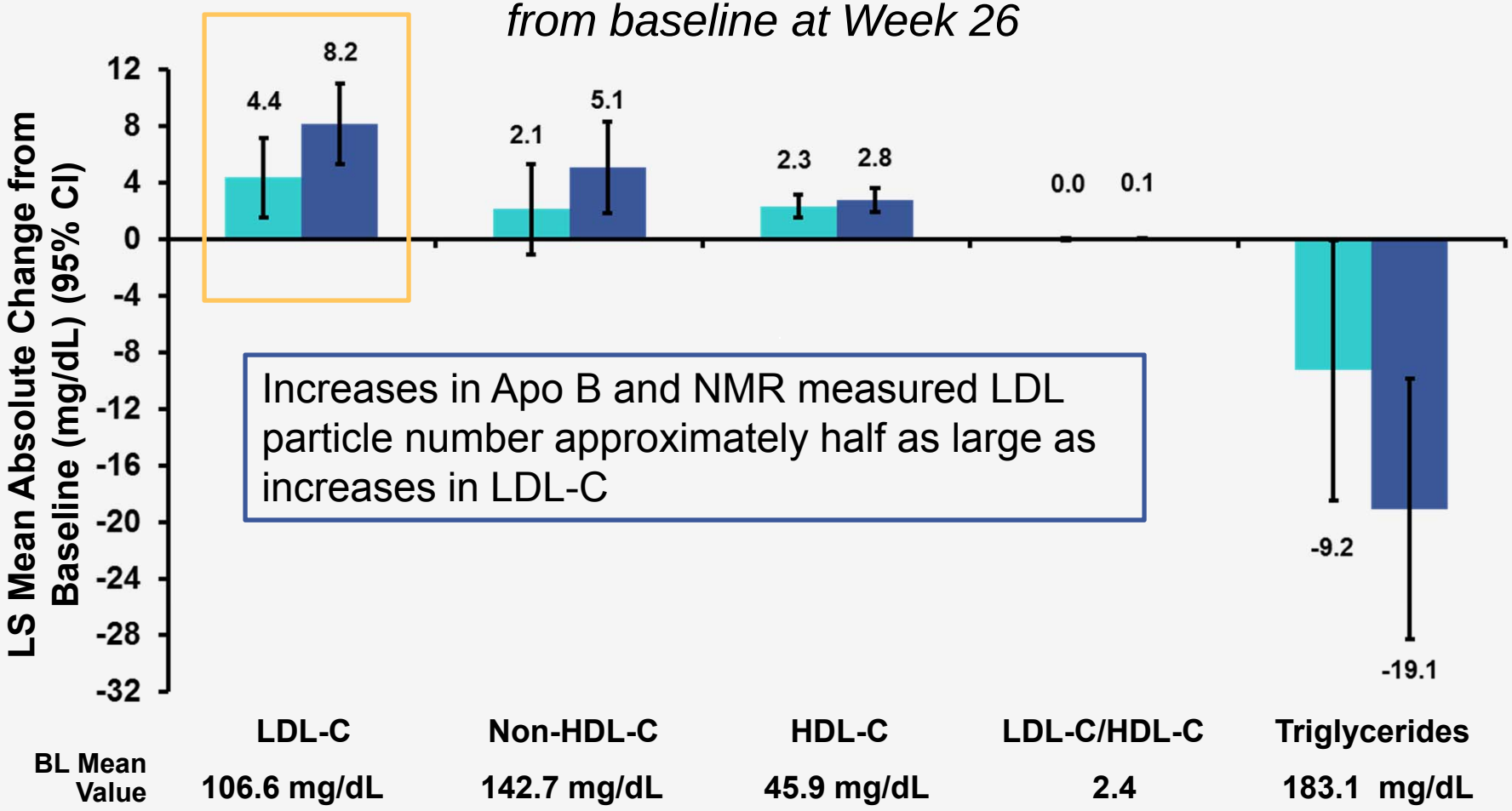
**CV Safety**

- **Changes in LDL-C**
- **CV Meta-analysis results**

# Fasting Lipids: Absolute Change

## Placebo-controlled Studies Dataset

*LS Mean placebo-subtracted absolute change from baseline at Week 26*



# CV Risk Factor Changes with Canagliflozin

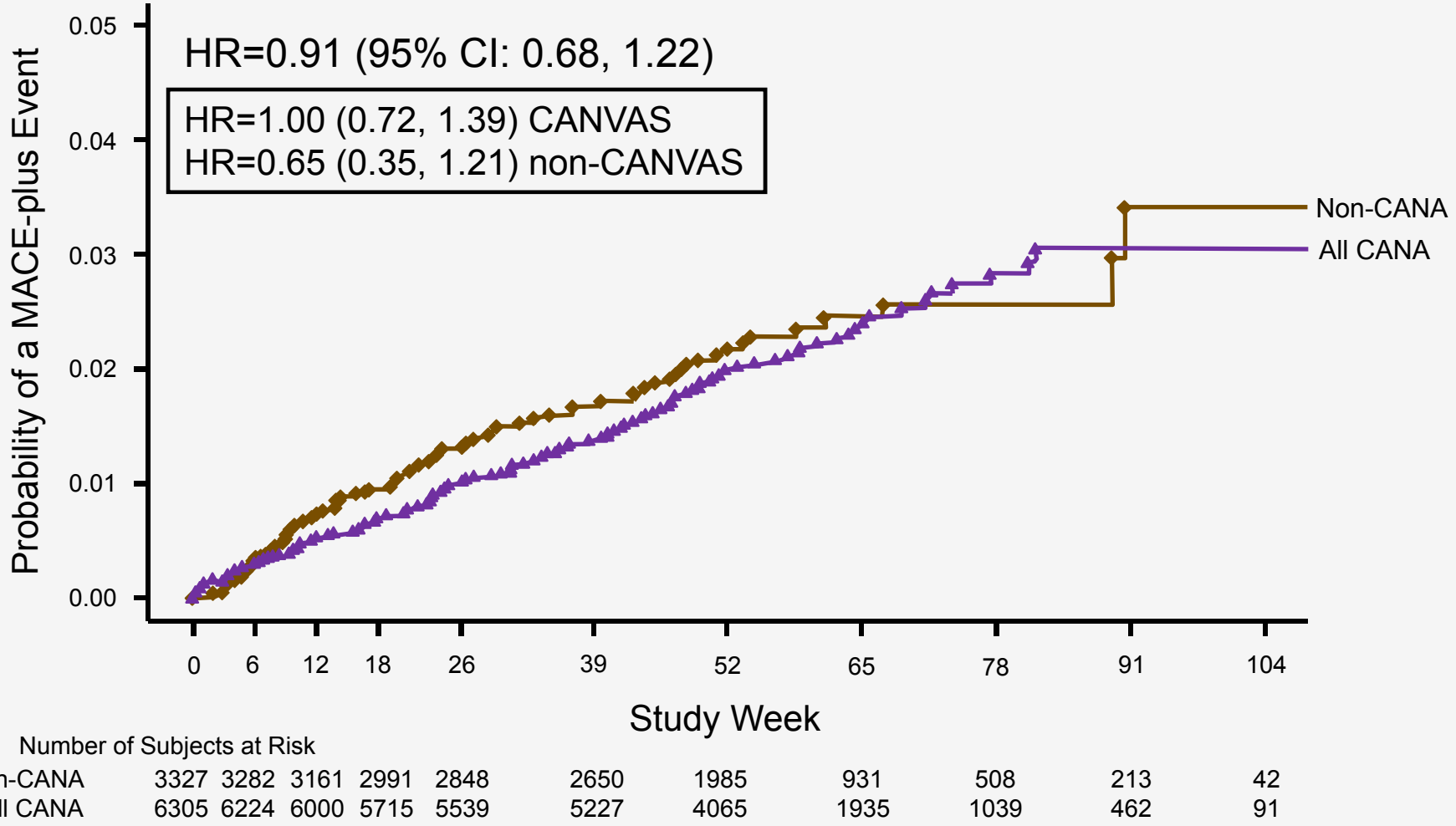
- Changes in fasting lipids
  - Increases in LDL-C
    - Smaller increases in non-HDL-C, Apo B, LDL particle number
  - Increases in HDL-C
  - No change in LDL-C/HDL-C ratio
  - Decreases in TG
- Decreases in systolic and diastolic blood pressure
- Improved glycemic control
- Decrease in body weight

# Pre-specified Cardiovascular Meta-analyses Procedures

- Predefined composite endpoint of “MACE-plus”: CV death, nonfatal MI, nonfatal stroke, hospitalized unstable angina
- Stepwise CV meta-analyses
(based upon FDA DM CV guidance, 2008)
  - Current step 1 to meet upper bound < 1.8 planned when 200 events
  - Step 2 to meet upper bound < 1.3 planned when 500 events
- Step 1 meta-analysis included 201 events from all Phase 2 and 3 studies completed prior to 02 FEB 2012
  - Events from CANVAS (161) and non-CANVAS studies (40)
- Blinded, independent adjudication committee operating under committee charter

# Time to Event Analysis for MACE-plus
## All Phase 2/3 Studies

*KM estimate*



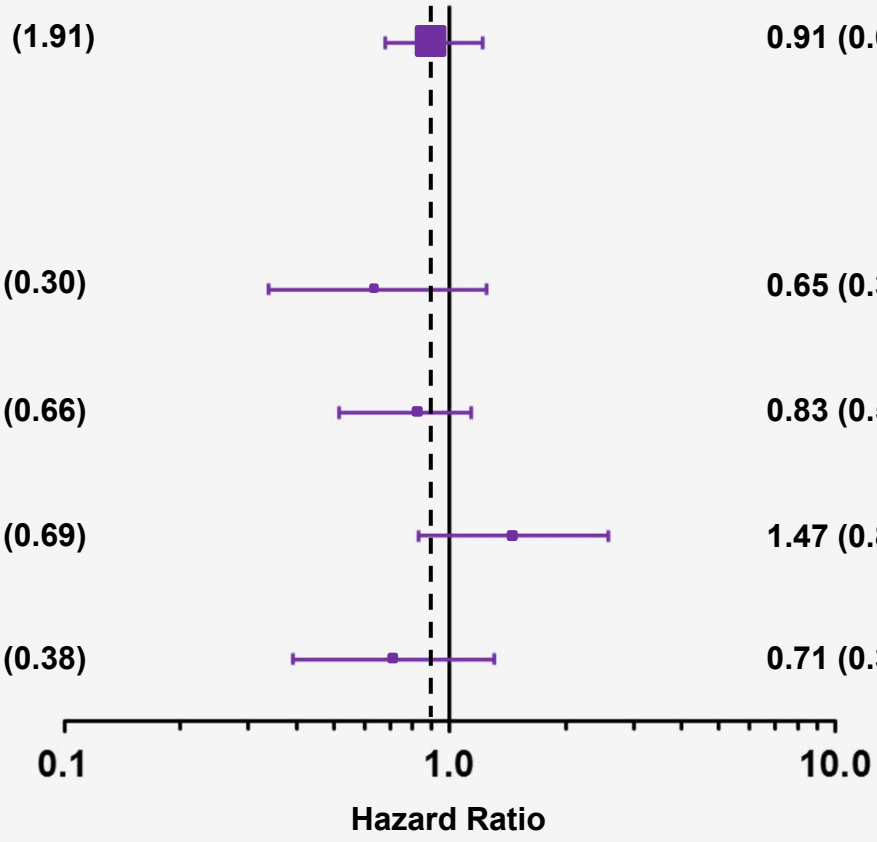

Number of Subjects at Risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Non-CANA | 3327 | 3282 | 3161 | 2991 | 2848 | 2650 | 1985 | 931 | 508 | 213 | 42 |
| All CANA | 6305 | 6224 | 6000 | 5715 | 5539 | 5227 | 4065 | 1935 | 1039 | 462 | 91 |

***Note**: includes all studies with data base lock prior to 31-Jan-12; mITT analysis set; events within 30 days of last dose*

# Incidence and HR for Adjudicated CV Events
## All Phase 2/3 Studies

| | Non-CANA Events/PYs (per 100 patient-yrs) | All CANA Events/PYs (per 100 patient-yrs) | Hazard Ratio Estimate (95% CI) |
|---|---|---|---|
| Primary Endpoint | 71/3467 (2.05) | 130/6821 (1.91) | 0.91 (0.68, 1.22) |
| CV Endpoint | | | |
| CV Death | 16/3496 (0.46) | 21/6888 (0.30) | 0.65 (0.34, 1.24) |
| FNF MI | 27/3484 (0.78) | 45/6864 (0.66) | 0.83 (0.52, 1.34) |
| FNF Stroke | 16/3489 (0.46) | 47/6859 (0.69) | 1.47 (0.83, 2.59) |
| Unstable angina | 18/3484 (0.52) | 26/6874 (0.38) | 0.71 (0.39, 1.30) |



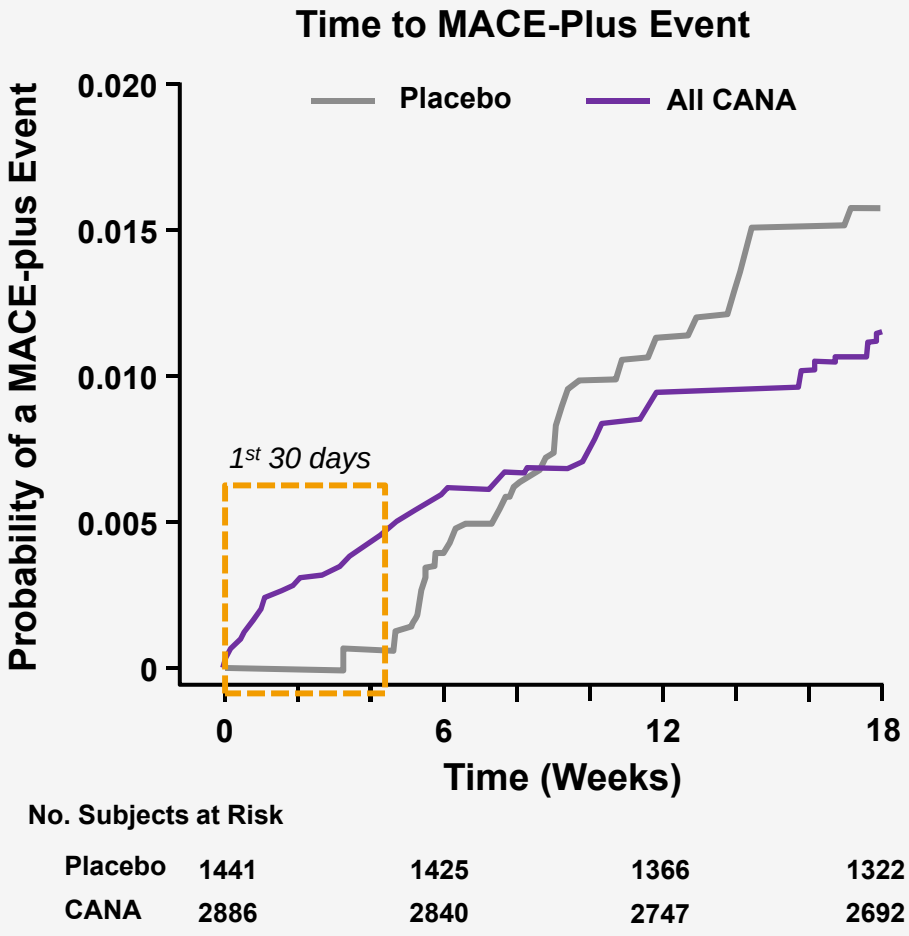
# CV Meta-analysis – Further Assessments

## Early Imbalance in CANVAS

## HR Differences by Event Type

# Early MACE-plus Events in CANVAS
# Assessment of Events in First 30 Days

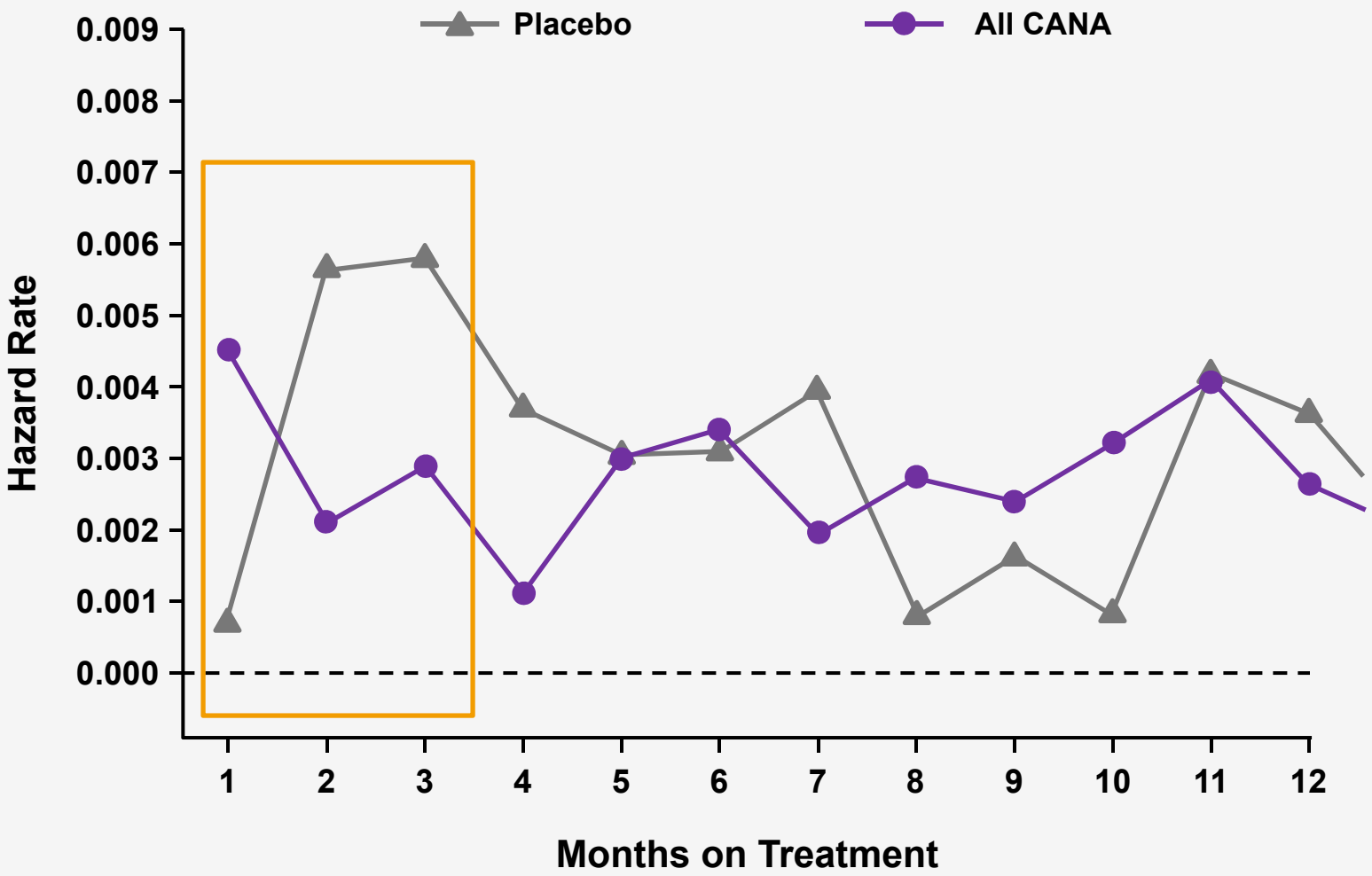
Issue: imbalance in 1st 30 days in CANVAS: 13 events in All CANA groups vs 1 event in PBO (2:1 rand)




*Assessment*

- Imbalance not seen in overall CV meta-analysis (pre-specified): 15 vs 5 in All CANA vs PBO (~ 2:1 rand)
- Considerable month-to-month variability in frequency of events
- Low rate in PBO group in 1st 30 days not typical in T2DM outcome studies
- Lack of association with volume depletion-related adverse events – time course or dose-relationship
- Subjects with "early" MACE+ events not more susceptible subset

# Estimated Hazard Function
## MACE-Plus CANVAS Study, mITT Analysis Set



# Initial Imbalance in Events in CANVAS Assessment

*Plausibility of association of MACE-plus and volume depletion:*

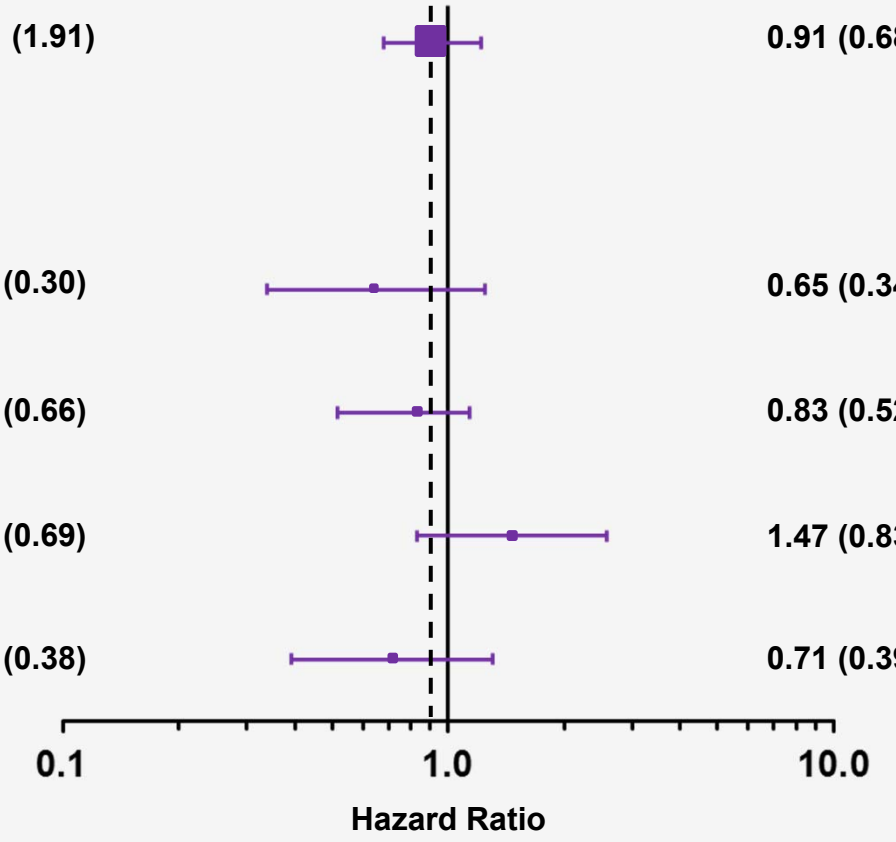
- Volume-related AEs increased over 1st ~ 90-120 days
  - vs MACE-plus events - higher rate in CANA group in 1st 30 days – then lower rate in next 60 days
- Volume-related AEs notably dose-related (300 mg > 100 mg)
  - vs MACE-plus events: 7 in 100 mg group / 6 in 300 mg group
- No reports of reduced intravascular volume-related AEs in subjects with MACE-plus events – or suggestive descriptions in narratives

*Conclusions*

- No evident relationship of MACE-plus to reduced intravascular-related AEs
- Early imbalance reflects the marked month-to-month variability

# Incidence and HR for Adjudicated CV Events
## All Phase 2/3 Studies

| | Non-CANA Events/PYs (per 100 patient-yrs) | All CANA Events/PYs (per 100 patient-yrs) | Hazard Ratio Estimate (95% CI) |
|---|---|---|---|
| Primary Endpoint | 71/3467 (2.05) | 130/6821 (1.91) | 0.91 (0.68, 1.22) |
| CV Endpoint | | | |
| CV Death | 16/3496 (0.46) | 21/6888 (0.30) | 0.65 (0.34, 1.24) |
| FNF MI | 27/3484 (0.78) | 45/6864 (0.66) | 0.83 (0.52, 1.34) |
| FNF Stroke | 16/3489 (0.46) | 47/6859 (0.69) | 1.47 (0.83, 2.59) |
| Unstable angina | 18/3484 (0.52) | 26/6874 (0.38) | 0.71 (0.39, 1.30) |

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# Assessment of Observed HR for Stroke

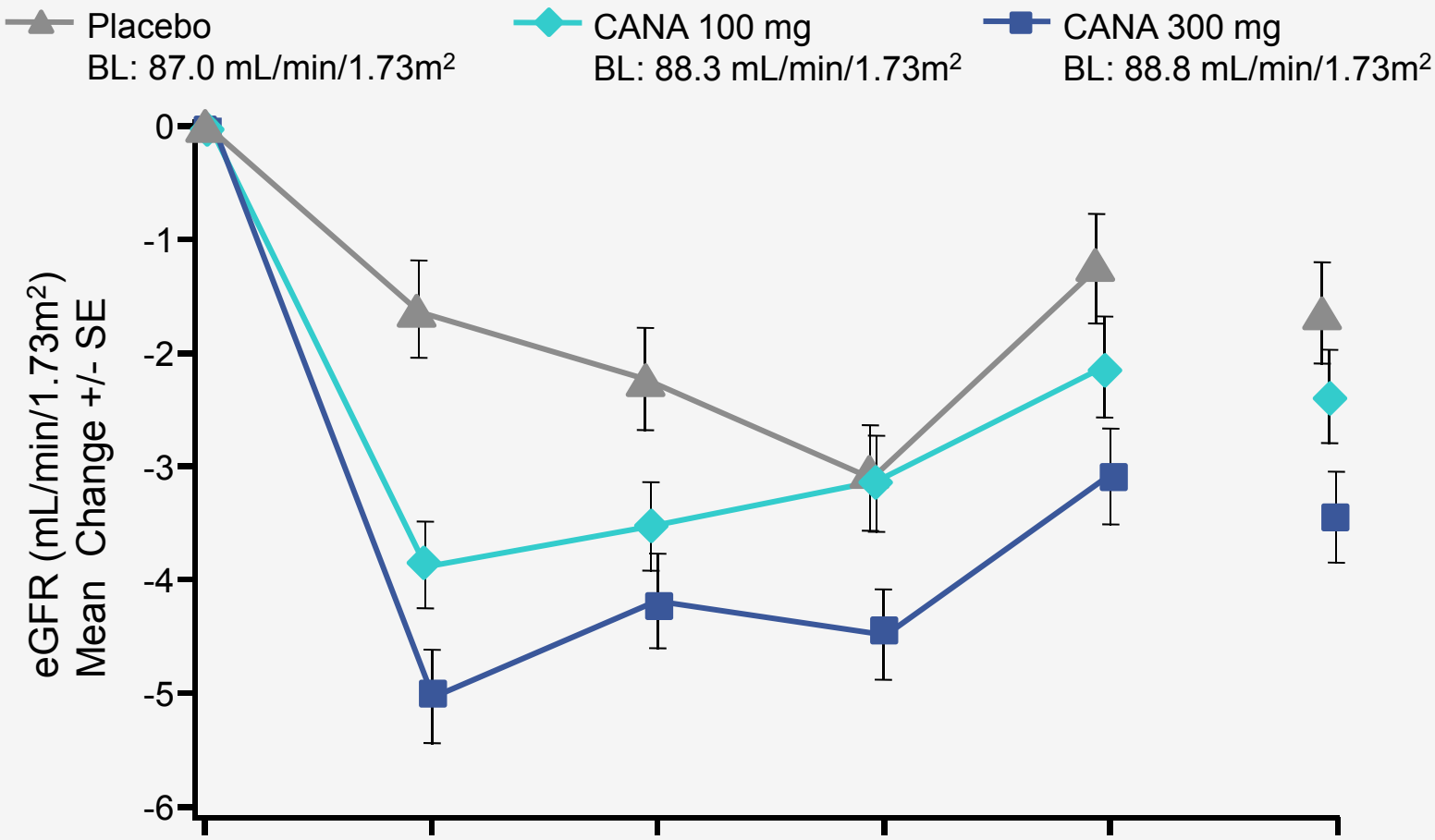
- Pre-specified composite provides most robust assessment
  - Variability expected in individual event types with smaller event number
- Assessment of plausibility of association with CANA due to dehydration with hypercoagulability
  - Minimal overlap with volume-related AEs, and decreases in SBP/increases in hemoglobin not notably different in subjects with stroke
  - Different time-course, lack of dose-relationship (vs volume-related AEs)
  - No difference in other events in stroke continuum: TIA  HR 0.99
  - No evidence of hypercoagulability
  - No reported increase in strokes with diuretics
- Assessment: reflects a chance difference, with further assessment of stroke HR over time appropriate

# Additional Key Safety Assessments

## Renal Safety Evaluations

- eGFR change from baseline
- Albumin / Creatinine Ratio (ACR)

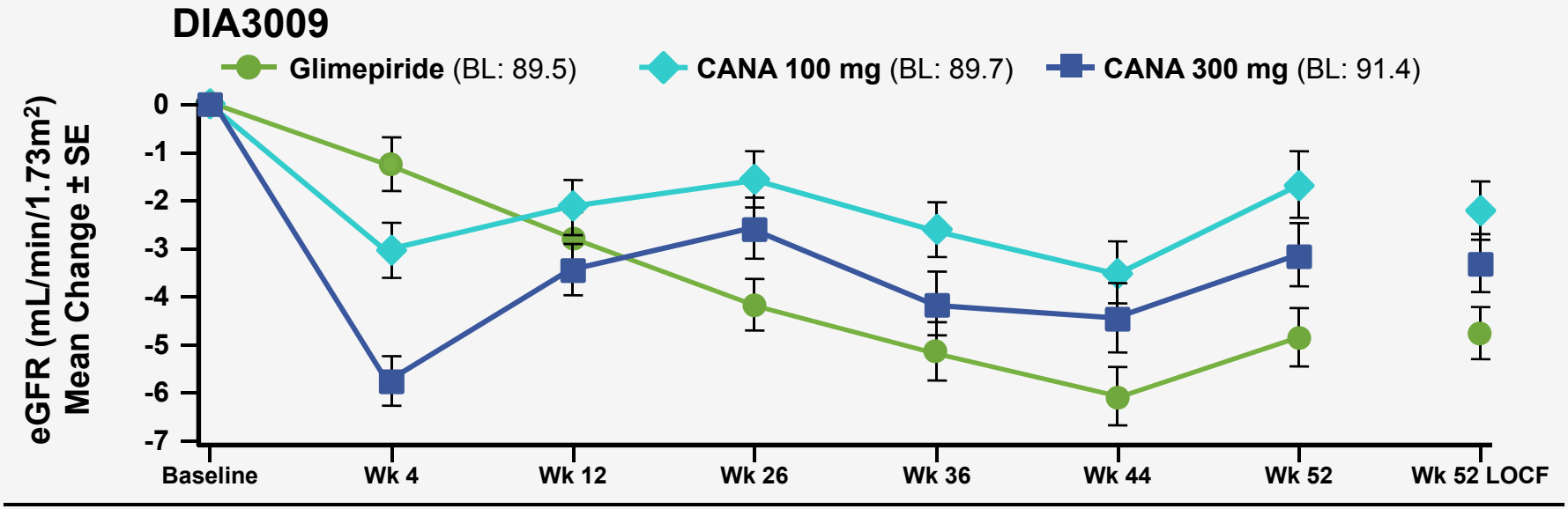
# Mean Change in eGFR from Baseline Over Time
## Placebo-controlled Studies Dataset

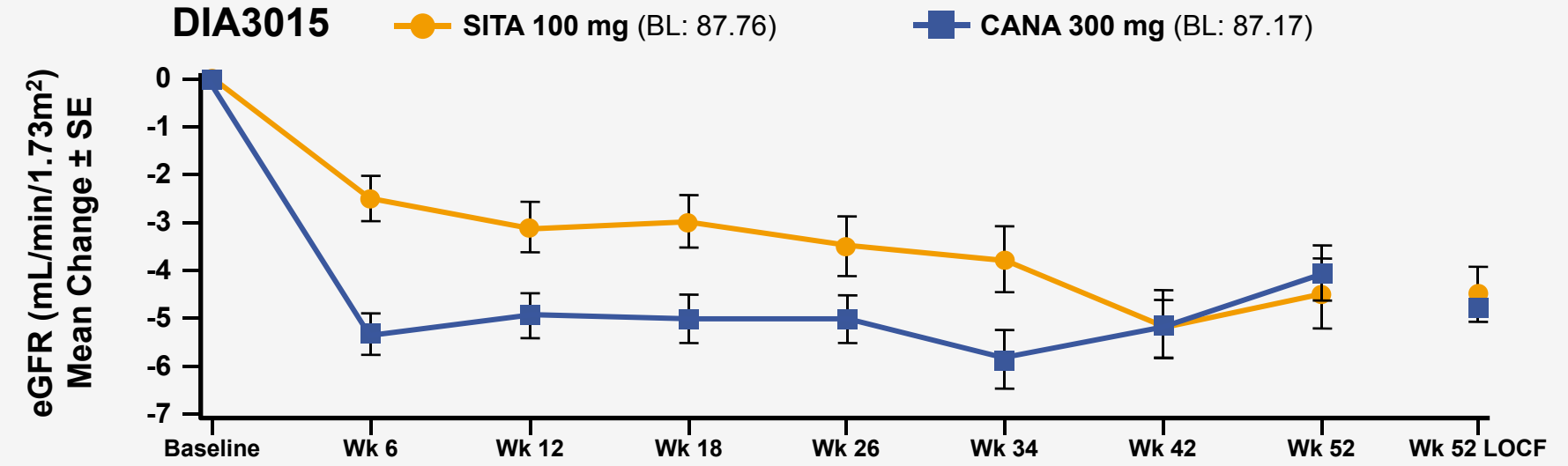



| N | Baseline | Wk 6 | Wk 12 | Wk 18 | Wk 26 | Wk 26 LOCF |
|---|---|---|---|---|---|---|
| Placebo | 646 | 620 | 590 | 560 | 526 | 624 |
| CANA 100 mg | 833 | 796 | 765 | 748 | 715 | 809 |
| CANA 300 mg | 834 | 795 | 758 | 744 | 720 | 805 |

# eGFR Mean Change from Baseline Over Time

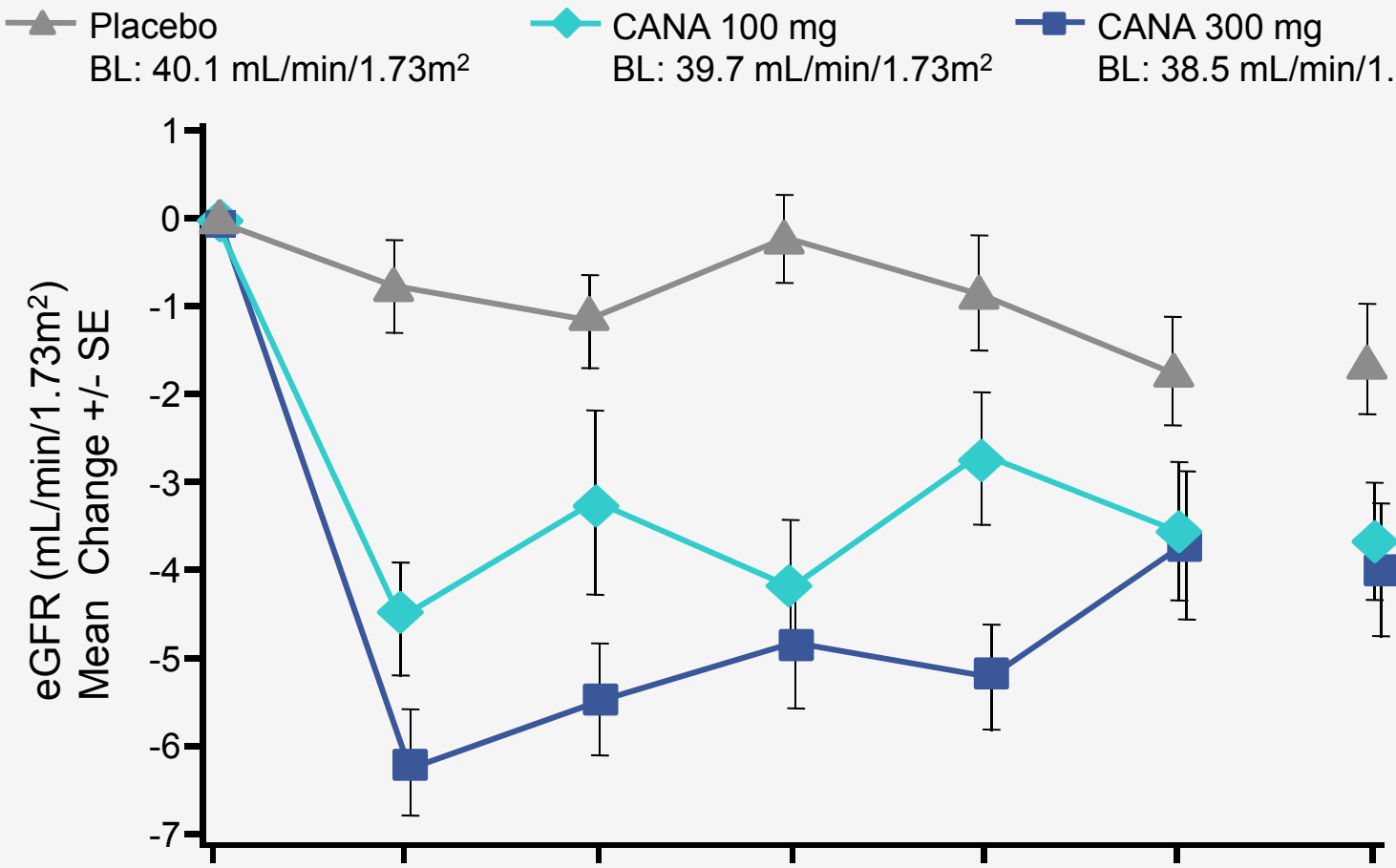
## Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009) and Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)



# Mean Change in eGFR from Baseline Over Time

## Study in Subjects with T2DM and Renal Impairment (DIA3004)

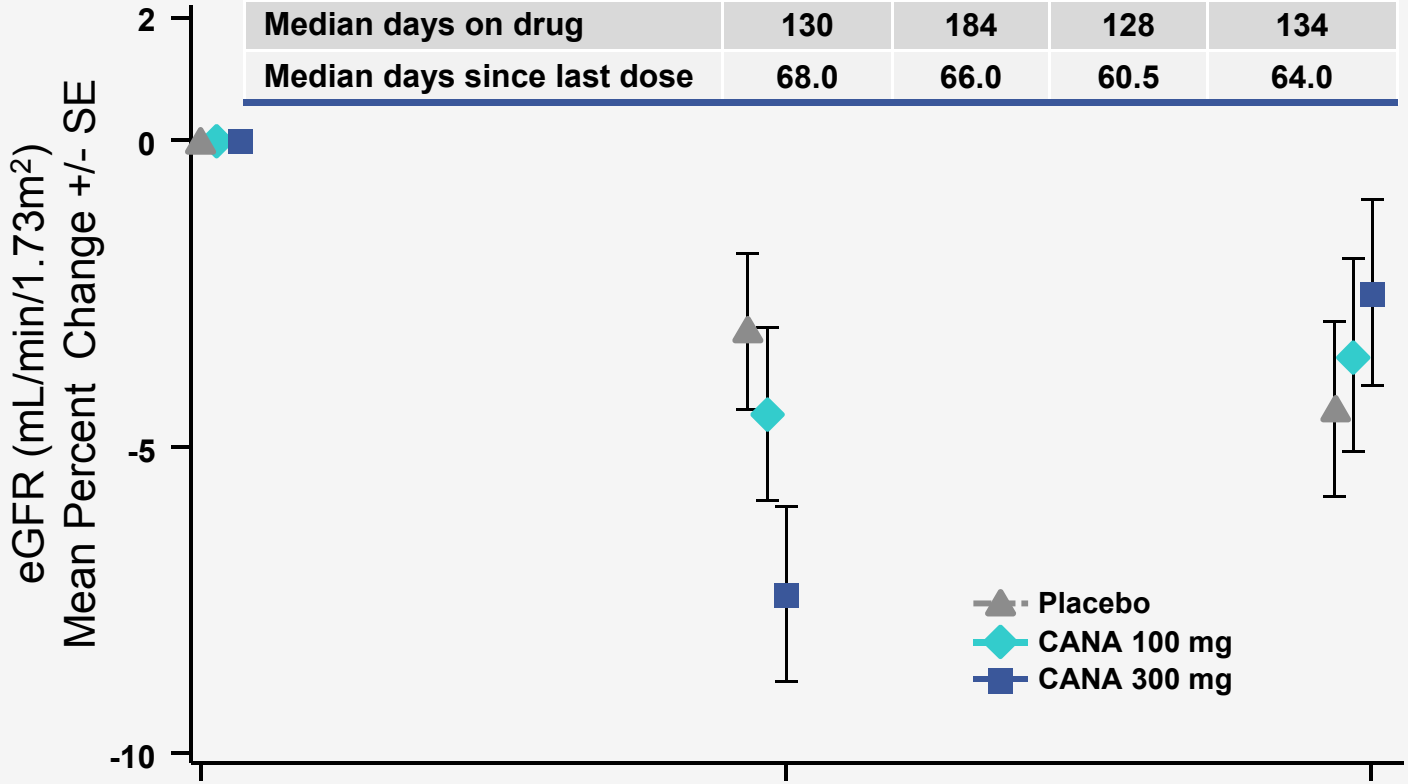



| N | Baseline | Wk 3 | Wk 6 | Wk 12 | Wk 18 | Wk 26 | Wk 26 LOCF |
|---|---|---|---|---|---|---|---|
| Placebo | 90 | 86 | 83 | 82 | 80 | 75 | 87 |
| CANA 100 mg | 90 | 86 | 84 | 79 | 77 | 72 | 89 |
| CANA 300 mg | 89 | 84 | 83 | 83 | 83 | 80 | 89 |

# Mean Percent Change in eGFR After Drug Discontinuation
## CV Safety Study (DIA3008 July 2012 Dataset)

**Baseline eGFR (mL/min/1.73m$^2$): 77**

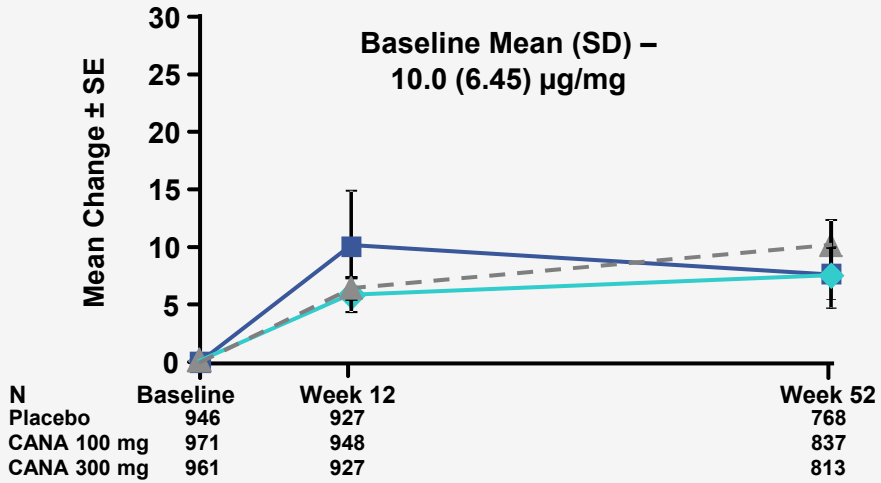
| | Placebo | CANA 100 mg | CANA 300 mg | All CANA |
|---|---|---|---|---|
| Median days on drug | 130 | 184 | 128 | 134 |
| Median days since last dose | 68.0 | 66.0 | 60.5 | 64.0 |




| N | Baseline | Last On Drug Value | Last Off Drug Value |
|---|---|---|---|
| Placebo | 140 | 140 | 140 |
| CANA 100 mg | 126 | 126 | 126 |
| CANA 300 mg | 130 | 130 | 130 |

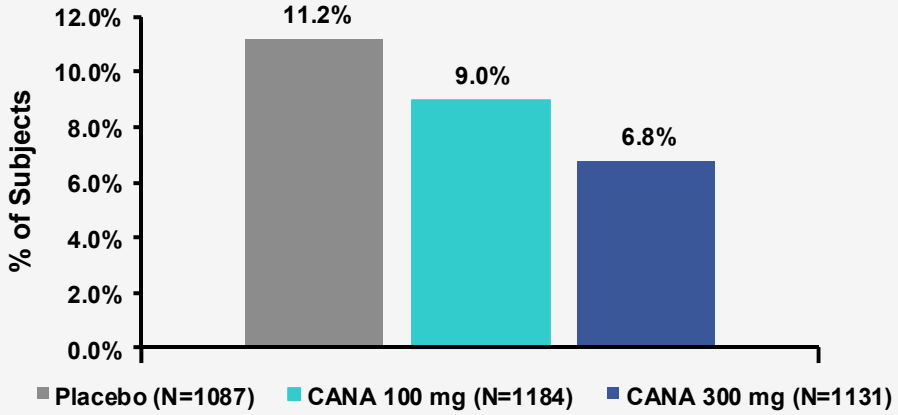
# Change from Baseline in Albumin/Creatinine Ratio
## CV Safety Study (DIA3008) through 01 Jul 2012

### Subjects with Normo-albuminuria

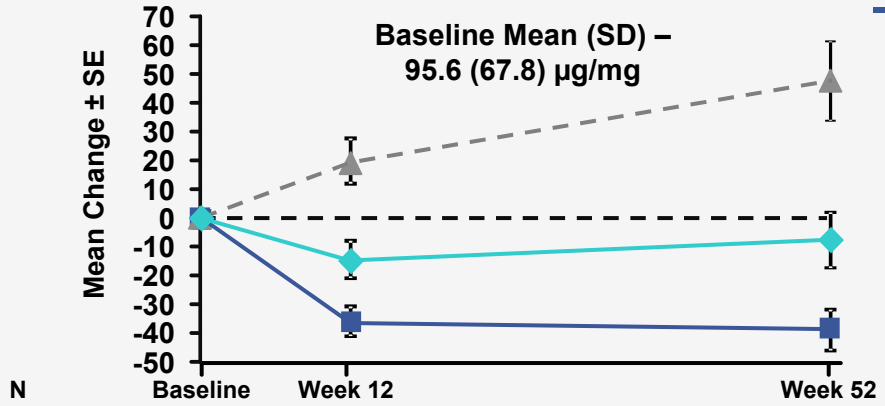



| N | Baseline | Week 12 | Week 52 |
|---|---|---|---|
| Placebo | 946 | 927 | 768 |
| CANA 100 mg | 971 | 948 | 837 |
| CANA 300 mg | 961 | 927 | 813 |

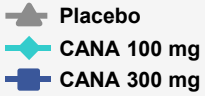
### Proportion Progressing ≥ 1-step



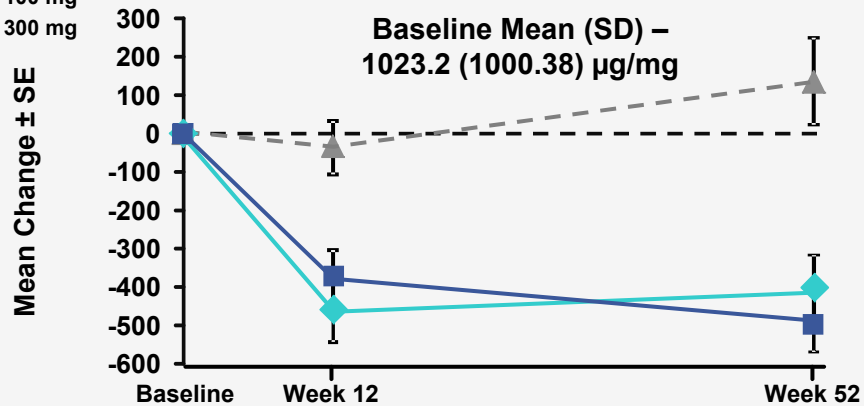

### Subjects with Micro-albuminuria




| N | Baseline | Week 12 | Week 52 |
|---|---|---|---|
| Placebo | 289 | 284 | 222 |
| CANA 100 mg | 320 | 311 | 269 |
| CANA 300 mg | 288 | 282 | 234 |




### Subjects with Macro-albuminuria




| N | Baseline | Week 12 | Week 52 |
|---|---|---|---|
| Placebo | 96 | 94 | 76 |
| CANA 100 mg | 72 | 71 | 63 |
| CANA 300 mg | 83 | 79 | 69 |

Within 2 Days After Last Study Medication

# Safety in Subjects with Stage 3 CKD (eGFR 30 to <60 mL/min/1.73 $m^2$)

# Baseline Characteristics
## Renal Impairment Dataset (eGFR 30 to <60)

| | Placebo-controlled Study N = 2313 | Renal Impairment Dataset N =1085 | Broad Dataset N =9439 | CANVAS N = 4327 |
|---|---|---|---|---|
| **Sex, n (%)** | | | | |
| Male | 49.5 | **58.4** | 58.2 | 66.1 |
| Female | 50.5 | **41.6** | 41.8 | 33.9 |
| **Age (y), Mean (SD)** | 56.0 (9.81) | **67.1 (7.67)** | 59.9 (9.35) | 62.4 (8.02) |
| **Race, n (%)** | | | | |
| White | 72.2 | **78.2** | 72.6 | 73.4 |
| Black or African-American | 5.1 | **2.9** | 3.8 | 2.4 |
| Asian | 12.3 | **13.0** | 15.8 | 18.4 |
| Other | 10.4 | **5.9** | 7.8 | 5.8 |
| **Body mass index, kg/m$^2$,Mean (SD)** | 32.1 (6.42) | **32.5 (6.12)** | 31.9 (6.06) | 32.1 (6.24) |
| **HbA1c (%), Mean (SD)** | 8.0 (0.93) | **8.1 (0.93)** | 8.0 (0.90) | 8.2 (0.92) |
| **Duration of diabetes (y), Mean (SD)** | 7.3 (6.04) | **15.1 (8.40)** | 10.6 (7.53) | 13.4 (7.52) |
| **eGFR, Mean** | 88 | **48** | 81 | 77 |
| **≥ 1 Microvascular Complication, %** | 18.9 | **59.1** | 33.1 | 44.2 |

Renal impairment dataset: subjects from DIA3004, DIA3005, DIA3008, and DIA3010 with baseline eGFR 30 to < 60 mL/min/1.73 m$^2$

# Summary of Adverse Events
## Renal Impairment Dataset (eGFR 30 to <60)

| | Placebo N=382 n (%) | CANA 100 mg N=338 n (%) | CANA 300 mg N=365 n (%) | All CANA N=703 n (%) |
|---|---|---|---|---|
| Any Adverse Events | 269 (70.4) | 250 (74.0) | 275 (75.3) | 525 (74.7) |
| AEs leading to discontinuation | 22 (5.8) | 19 (5.6) | 28 (7.7) | 47 (6.7) |
| Serious AEs | 75 (19.6) | 45 (13.3) | 54 (14.8) | 99 (14.1) |
| Serious AEs leading to discontinuation | 14 (3.7) | 9 (2.7) | 12 (3.3) | 21 (3.0) |
| Death | 6 (1.6) | 3 (0.9) | 5 (1.4) | 8 (1.1) |

# Incidence of Adverse Drug Reactions
## Renal Impairment Dataset (eGFR 30 to <60)

| | Placebo N=382 n (%) | CANA 100 mg N=338 n (%) | CANA 300 mg N=365 n (%) | All CANA N=703 n (%) |
|---|---|---|---|---|
| Osmotic diuresis-related AEs | 14 (3.7) | 14 (4.1) | 14 (3.8) | 28 (4.0) |
| Reduced intravascular volume-related AEs | 10 (2.6) | 17 (5.0) | 31 (8.5) | 48 (6.8) |
| Urinary tract infection AEs | 23 (6.0) | 21 (6.2) | 27 (7.4) | 48 (6.8) |

| Female Subjects | Placebo N=156 n (%) | CANA 100 mg N=140 n (%) | CANA 300 mg N=155 n (%) | All CANA N=295 n (%) |
|---|---|---|---|---|
| Genital mycotic infection AEs | 3 (1.9) | 15 (10.7) | 15 (9.7) | 30 (10.2) |

| Male Subjects | Placebo N=226 n (%) | CANA 100 mg N=198 n (%) | CANA 300 mg N=210 n (%) | All CANA N=408 n (%) |
|---|---|---|---|---|
| Genital mycotic infection AEs | 3 (1.3) | 5 (2.5) | 15 (7.1) | 20 (4.9) |

# Renal Function and Electrolyte Changes in Subjects with Stage 3 CKD

- Renal function
  - Larger initial percentage decrease in eGFR, then rise in eGFR towards baseline
    - Reversibility after discontinuation (DIA3008)
  - Outlier analyses shows similar pattern as seen in Broad Dataset
  - No increase in renal-related SAEs or AEs leading to D/C
  - Decrease in the urinary albumin creatinine ratio (DIA3004)
- Electrolytes
  - Modest mean increases in serum phosphate and magnesium
    - Low incidence of values meeting outlier criteria (> 25% above ULN), and no AEs reported
  - No relevant mean changes in serum potassium
    - Infrequent hyperkalemia – generally related to multiple factors including CKD + ACE inhibitors/ARBs + other agents (eg, aliskerin)

# Additional Key Safety Assessments

## Bone Safety

- Calcium, phosphate, 1-25 dihydroxy-vitamin D, and PTH
- Bone density assessment (DXA)
- Incidence of fractures

# Changes in Calcium Axis

- No meaningful mean changes in serum calcium or urine calcium excretion
- Small mean increases in serum phosphate and magnesium (5-10%) – stable over time
- Transient increase in PTH at Week 3 with no substantive changes at Week 12 (Phase 2), or at Weeks 26 or 52 (Phase 3)
  - No increase in PTH in Stage 3 CKD subjects (DIA3004) – small decrease relative to placebo over 26 weeks
- Variable, but overall not meaningful changes in 1,25-dihydroxyvitamin D levels

# Percent Change in BMD Results at Week 52 by DXA
## Study in Older Subjects with T2DM (DIA3010)

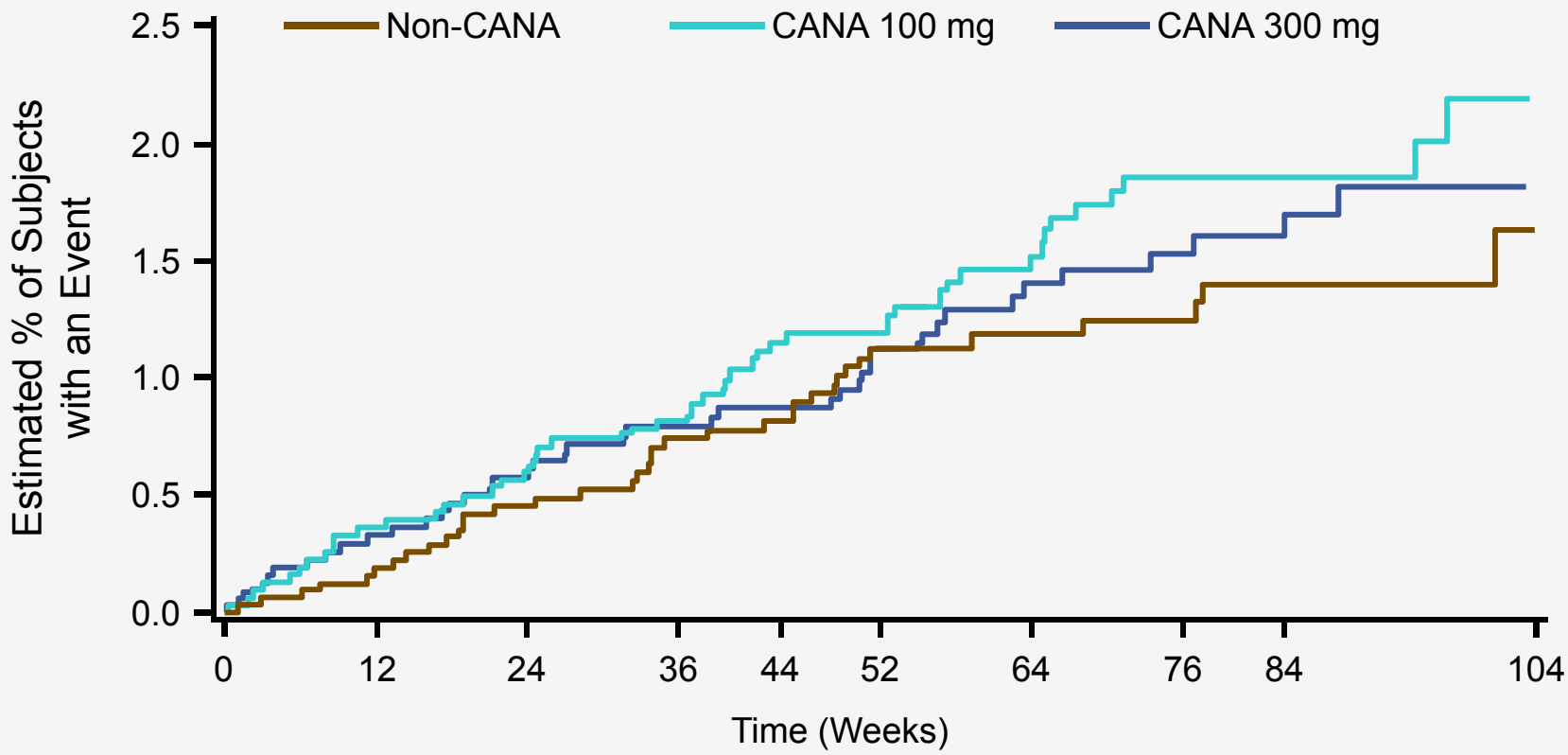
| Site | CANA 100 mg Pbo-subtracted Mean (95% CI) N=241 | CANA 300 mg Pbo-subtracted Mean (95% CI) N=236 |
|---|---|---|
| Lumbar spine | -0.4 (-1.0, 0.3) | -0.7 (-1.4, -0.1) |
| Total hip | -0.4 (-1.0, 0.1) | -0.7 (-1.3, -0.2) |
| Femoral neck | 0.1 (-0.6, 0.8) | 0.6 (-0.1, 1.4) |
| Distal forearm | 0.5 (-0.1, 1.2) | 0.1 (-0.6, 0.7) |

# Adjudicated Fractures
## Broad Dataset through 01 Jul 2012

| | Non-CANA N=3262 | CANA 100 mg N=3092 | CANA 300 mg N=3085 | All CANA N=6177 |
|---|---|---|---|---|
| Subjects with **adjudicated fracture** event n (%) | 53 (1.6) | 68 (2.2) | 61 (2.0) | 129 (2.1) |
| *Incidence rate/1000 person years exposure (SE)* | *13.17 (1.83)* | *16.69 (2.04)* | *15.30 (1.98)* | *16.00 (1.41)* |
| Between group (vs Non-CANA) difference in incidence rate (95% CI) | - | 3.5 (-1.85; 8.88) | 2.1 (-3.14; 7.4) | 2.8 (-1.7; 7.36) |
| Subjects with **adjudicated low trauma** fracture n (%) | 38 (1.2) | 51 (1.6) | 48 (1.6) | 99 (1.6) |
| *Incidence rate/1000 person years exposure* | *9.44 (1.55)* | *12.51 (1.77)* | *12.04 (1.76)* | *12.28 (1.24)* |
| Between group (vs Non-CANA) difference in incidence rate (95% CI) | - | 3.1 (-1.54; 7.68) | 2.6 (-2.00; 7.19) | 2.8 (-1.06; 6.73) |

# Time to First Low Trauma Fracture AE
## Broad Dataset through 01 Jul 2012

*KM Estimate*




| Number Subjects at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-CANA | 3262 | 3113 | 2880 | 2700 | 2602 | 2523 | 1650 | 1313 | 1004 | 351 |
| CANA 100 mg | 3092 | 2971 | 2820 | 2702 | 2617 | 2571 | 1781 | 1418 | 1079 | 378 |
| CANA 300 mg | 3085 | 2924 | 2754 | 2635 | 2563 | 2511 | 1720 | 1377 | 1043 | 376 |

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# Summary of Safety and Tolerability

- Large Phase 3 program with >10,000 subjects randomized
  - Substantial proportion of vulnerable individuals studied
- Overall well tolerated at both doses of canagliflozin
  - Low rate of discontinuations due to adverse events
  - Incidence of SAEs and deaths comparable to control
  - Safety and tolerability profile similar across range of eGFR (> 30 mL/min/1.73 $m^2$)

# Summary of Safety and Tolerability (cont.)

- Specific adverse drug reactions characterized
  - Genital mycotic infections and UTIs
  - Osmotic diuresis-related (thirst, polyuria, frequency)
  - Reduced intravascular volume AEs higher at 300 mg than at 100 mg, with risk factors identified
  - Hypoglycemia with insulin or sulphonylurea agents
  - Other including constipation and uncommon events of urticaria/rash
- Specific safety assessments performed showed
  - Increase in LDL-C; CV HR 0.91 with upper bound of 1.22 (<1.8)
  - Small, transient, and reversible decreases in eGFR consistent with the hemodynamic effect of canagliflozin
  - Small decrease in BMD (likely related to weight loss), small numerical imbalance in fractures

# Summary of Efficacy

- Consistent and sustained dose-related improvements in glucose control with a low incidence of hypoglycemia
  - Reductions in $HbA_{1c}$, demonstrated non-inferior to glimepiride and sitagliptin and superior at 300 mg to both agents
  - Greater proportion to $HbA_{1c}$ goals
  - Fasting and post-meal glucose
- Improvements in beta-cell function (fasting and post-meal)
- Reductions in systolic blood pressure and in body weight

# Canagliflozin: Dosing Recommendations

In patients with T2DM (with an eGFR of >30 mL/min/1.73m$^2$) who need improved glycemic control

- Canagliflozin 100 mg or 300 mg
  - Starting dose of 100 mg in patients with eGFR <60 mL/min/1.73m$^2$, loop diuretics, or age ≥75 years
  - If inadequate response in patients started on 100 mg, increase to 300 mg dose

# Canagliflozin Benefit/Risk Assessment

**John Gerich, MD**
Professor Emeritus
University of Rochester Medical Center

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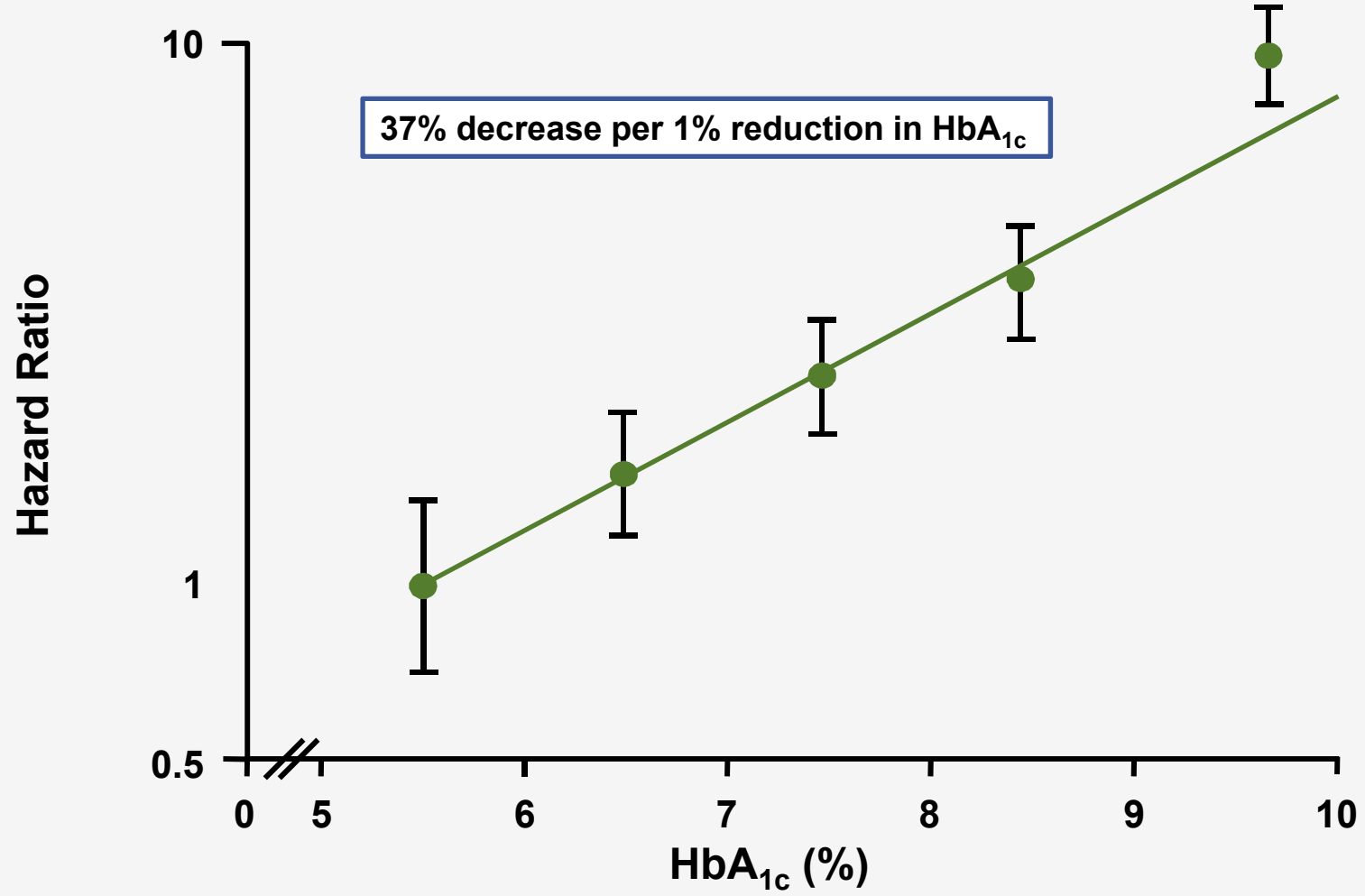
# Reduction in $HbA_{1c}$ Reduces Risk of Microvascular Disease




Stratton IM et al. *BMJ*. 2000;321(7258):405-412.

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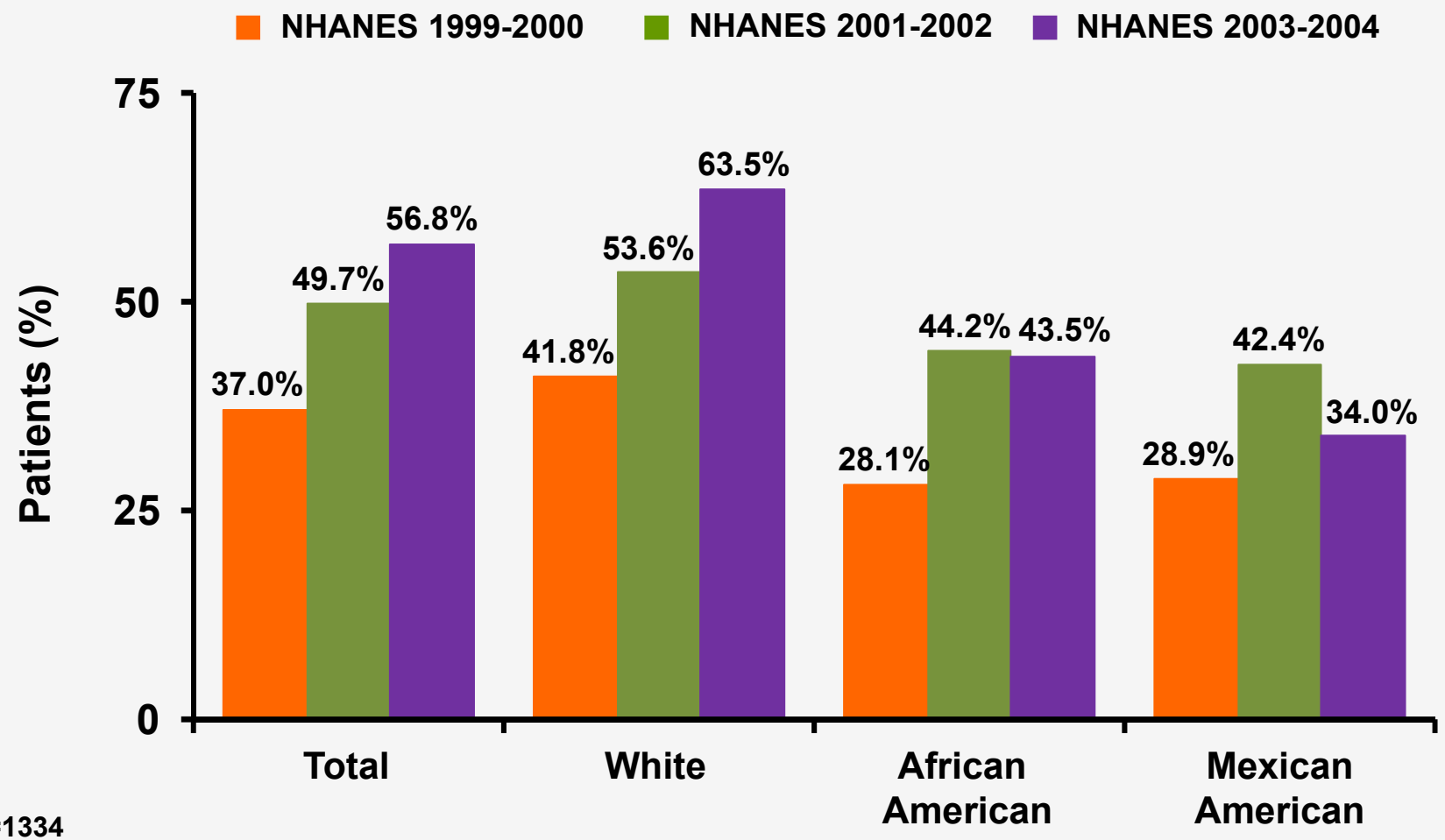
# Glycemic Control Has Improved – But Many Patients Still Not at Goal $HbA_{1c}$ <7%




**N=1334**
**NHANES=National Health and Nutrition Examination Survey**

Data from Ford E, et al. *Diabetes Care*. 2008;31(1):102-104.

# Limitations of Current Treatments for Patients with T2DM

- 5 classes of oral agents – 2 classes of SQ agents are recommended by ADA/EASD
- Limitations of currently available classes
  - Limited efficacy or durability: sulphonylurea (SU) agents, DPP-4 inhibitors
  - Hypoglycemia: SU agents, insulin
  - Weight gain: SU agents, PPARγ agents, insulin
  - GI side effects: metformin, GLP-1 agonists
  - Fluid retention: SU agents, PPARγ agents, insulin

<u>Conclusion: there is a need for new agents / new options</u>

# Benefit/Risk Profile of Canagliflozin

| Benefits | Risks |
|---|---|
| Robust, consistent, and sustained HbA1c-lowering, with low incidence of hypoglycemia | Increase in genital mycotic infections |
| Unique MOA – combinable/ complementary with other AHAs | Small increase in UTIs without increase in upper UTIs or SAEs |
| Improves beta-cell function | Dose-related higher incidence of reduced volume-related events |
| Weight loss | Dose-related increase in LDL-C |
| Reduction in blood pressure | Small reduction in BMD |
| Simple to administer, with once-daily oral dosing | |
| Flexible dosing (100 mg and 300 mg) | |

# Canagliflozin Summary

- Flexible dosing (100 and 300 mg) to meet the needs of different patients
- Favorable Benefit/Risk profile
- Valuable addition to address the unmet medical need of patients with type 2 diabetes